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GASTROENTEROLOGY

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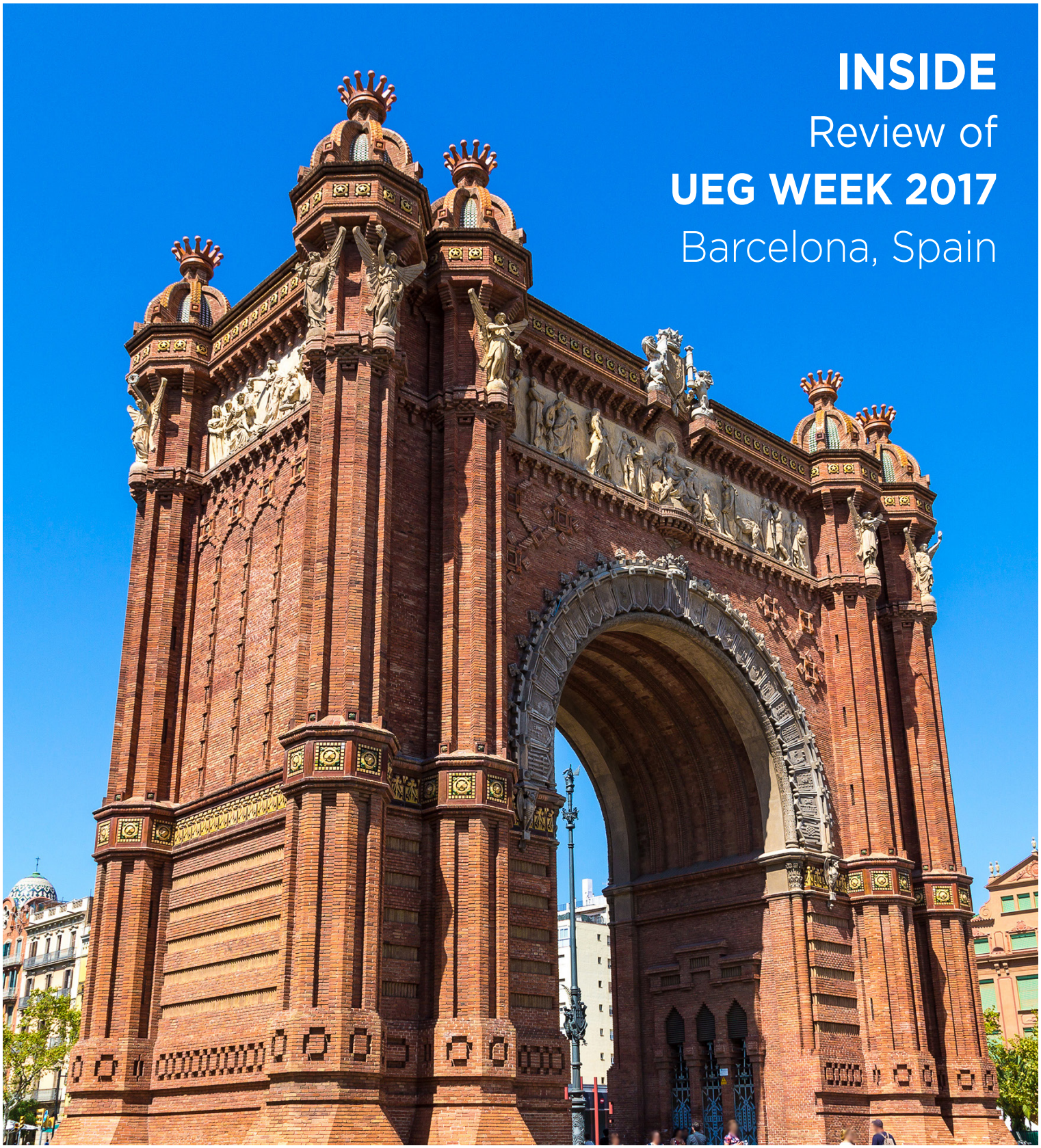

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Barcelona, Spain

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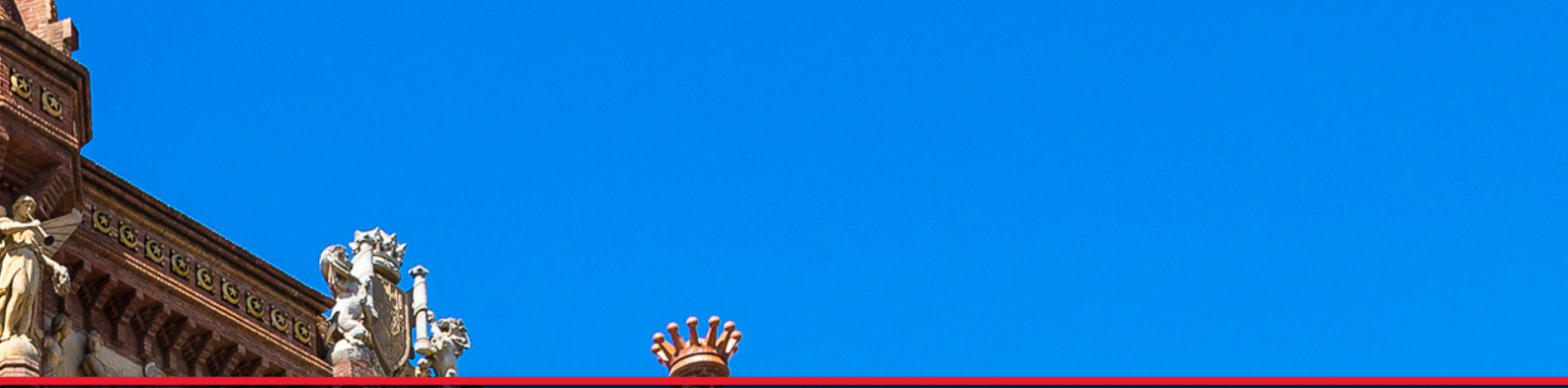

GASTROENTEROLOGY

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GASTROENTEROLOGY 6.1
DECEMBER 2017

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Welcome

Welcome to the 2017 edition of *EMJ Gastroenterology*, from which you will acquire new, exciting information on the gastroenterological happenings of the last year. Enclosed is an independent summary of this autumn's United European Gastroenterology (UEG) Week, which was attended by 12,810 participants from 116 countries and held in Barcelona, Spain. Following this, we present to you a selection of high-quality peer-reviewed papers, in addition to a series of abstract reviews from experts in the field of gastroenterology.

The 5-day event, held in one of the largest and most modern venues in Europe, the Fira Gran Via Conference Center, covered a wide range of topics during 208 captivating scientific sessions. The congress revisited the 'Today's Science, Tomorrow's Medicine' lecture series, with this year's focus being 'Host Microbiota Crosstalk'. Information presented in the >2,340 abstracts and overview lectures outlined the importance of the gut microbiota in both health and disease.

To complement our Congress Review section, we have included insights into the roles of toll-like receptor 5 in liver and pancreatic stellate cells, and an analysis of gastrostomy methods for nutritional support in gastroparesis, which are just two of a multitude of compelling topics covered in our Abstract Review section. Additionally, we present interviews with members of our highly regarded Editorial Board, who share personal experiences, discuss challenges within the field, and reflect on future directions.

"Additionally, we present interviews with members of our highly regarded Editorial Board, who share personal experiences, discuss challenges within the field, and reflect on future directions."

Our Editor's Pick for *EMJ Gastroenterology 6.1*, penned by Mandavdhare et al., is a thorough review of the recent advances in diagnosis and management of abdominal tuberculosis (ATB). The authors begin by outlining ATB and its clinical presentation, and then elucidate its resemblance to Crohn's disease, a condition that is increasingly recognised in countries where ATB is prevalent. Finally, the authors review advances in diagnosis and therapeutics, particularly regarding the ability to differentiate ATB from Crohn's disease. You will also find an article by Omodele-Lucien and Goren on the potential associations between *Helicobacter pylori* infection and the development of non-gastric gastrointestinal diseases, which establishes the nature of these relationships and the implications of *H. pylori* eradication from a clinical perspective.

The field of gastroenterology is ever-developing, so we hope this eJournal reflects this progression and that you find this year's edition as informative as we do. We look forward to seeing you all at next year's UEG Week congress in Vienna, Austria.

Spencer Gore

Director, European Medical Journal

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Foreword

Dr Jan Bornschein

John Radcliffe Hospital, Oxford University Hospitals, NHS Foundation Trust Oxford, UK

Dear Colleagues,

It is my great pleasure to introduce you to the 2017 edition of *EMJ Gastroenterology*. In this new issue, we will look back on a very exciting year that has brought us fantastic scientific research, great clinical advances, and has opened new perspectives for the future of European medicine.

The political agitation that has swept across Europe in the last 18 months has created a feeling of uncertainty as to the future of both active clinical healthcare as well as medical science; however, the 25th United European Gastroenterology Week, held in Barcelona, Spain during the peak time of political turbulence in Catalonia, has proven that we need not worry. With >15,000 participants, gastroenterologists from all over the world had the opportunity to experience an outstanding, well-balanced combination of state-of-the-art lectures, high-end research, and interactive panel discussions, which dealt with both the political representation of gastroenterology as a core healthcare provider and the future of clinical and scientific studies. European gastroenterology set a landmark in demonstrating unity across the continent, despite all political unrest. The support for young clinicians and scientists was recognisably a core aim of the conference, enabling networking and fruitful collaboration. Please see our congress review section for further details, wherein the editor's pick of hot topics is summarised for your convenience.

Once again, this year's edition of *EMJ Gastroenterology* delivers a great spectrum of expert reviews on topics of high clinical relevance. Mandavdhare et al. deliver a detailed overview of the manifestation of extrapulmonary tuberculosis, which is showing a rising incidence, not only as a result of increasing migration. The article outlines clinical pitfalls, relevant differential diagnoses, and the challenges in the treatment of the disease. Omodele-Lucien and Goren present a summary on the impact of *Helicobacter pylori* infection in the gastrointestinal and hepatobiliary system beyond gastric pathology, while Yeung and Lee compare the recent trends of *H. pylori* infection in the east and the west of the world, with emphasis on the clinical impact of the infection in children. Lahner et al. summarise current knowledge on atrophic body gastritis, with a special focus on the differential aetiology of this inflammation, the clinical consequences, and the modern options for diagnosis, and Lesmana et al. review current knowledge on the 'young' entity of non-alcoholic fatty pancreas disease and surveillance strategies for early detection of pancreatic cancer. Lastly, Emile and Elfeki present a comprehensive literature review of the postoperative, as well as the long-term, effects of sleeve gastrectomy on nutrition, and highlight the clinical impact of deficiency of certain nutrients.

I hope that you will find the articles in *EMJ Gastroenterology 6.1* stimulating from both a clinical and a scientific perspective.

With best regards,

Jan Bornschein

Locum Consultant Gastroenterologist, Oxford University Hospitals, NHS Foundation Trust Oxford, UK.

EMJ EUROPEAN MEDICAL JOURNAL

EMJ Hepatology 5.1 2017 Available Now

Includes a selection of the latest features, articles, interviews, and a full review of ILC 2017.

Featured inside:

CONGRESS REVIEW

Review of the 52nd International Liver Congress™ 2017, held in Amsterdam, Netherlands, 19th–23rd April 2017

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With *EMJ Hepatology* Editorial Board

SYMPOSIUM REVIEW

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Special Poster Feature: American Association for the Study of Liver Diseases (AASLD): The Liver Meeting® 2016 Coverage

- Chris Ontiveros

Beta-Blockers in Prevention of Development of Varices and Variceal Bleeding in Cirrhosis: Current Management, Controversies, and Future Directions

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Part 1: Epidemiology, Risk Factors, Pathogenesis, and Pathology

Part 2: Clinical Presentation and Diagnosis

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- Lior Charach et al.

A Look at Platelet Count in Chronic Hepatitis C Infection

- Romeo-Gabriel Mihăilă

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UEG WEEK 2017

FIRA GRAN VIA,
BARCELONA, SPAIN
28TH OCTOBER – 1ST NOVEMBER 2017

Welcome to the European Medical Journal review of the 25th Annual Meeting of the United European Gastroenterology Week

Citation: EMJ Gastroenterol. 2017;6[1]:12-23. Congress Review.

The United European Gastroenterology (UEG) Week celebrated its 25th anniversary at this year's congress, held in Barcelona, Spain, from the 28th October–1st November 2017. Known for embracing both art and culture with its quirky architecture and breathtaking historic monuments, Barcelona played the perfect host for this jubilee meeting.

The venue, the Fira Gran Via Conference Center, is one of the largest and most modern centres in Europe; with a whopping 4,957m^2 of the conference centre dedicated to UEG Week. The Fira Gran Via provided the perfect setting for the best networking and educational opportunities for healthcare professionals and researchers alike.

The 25th UEG Week accumulated the highest quality medical research, with participants from 116 different countries. Goals of the congress included raising awareness of digestive health, improving clinical standards, and promoting educational excellence in both clinical and scientific disciplines, and a myriad of topics were presented for all attendees to enjoy. A total of 2,341 abstracts, 1,963 posters, and 378 oral presentations were presented to the 12,810 attendees and 1,316 online spectators: truly impressive figures all-round. Some of the findings presented at the event are summarised in our Congress Review stories below, and include some exciting insights into the benefits of aspirin use, the discovery of reduced risk of gastric cancer following *Helicobacter pylori* treatment, and results from the latest clinical trials focussing on treatments for pancreatic neuroendocrine tumours and premalignant intraductal pancreatic mucinous tumours.

The opening ceremony began with some traditional Spanish music, setting the scene whilst welcoming all attendees to the fantastic event. UEG President Prof Michael Manns and UEG Scientific Committee Chair Dr Magnus Simrén introduced the week. Dr Simrén expressed his fondness for the annual meeting: "Just like previous years, I am extremely proud of our scientific programme, composed by the hardworking scientific committee, and I am convinced that all of you will find many of our sessions to be of interest to you." Prof Manns then welcomed experts from within digestive health care and research, each of whom

provided presentations of the latest advances in the field, within their special, invited lectures.

Awards were presented to individuals for their dedication and contributions to the field, including the UEG Lifetime Achievement Award, given to Prof Antony Axon, who has dedicated 40 years of his life to clinical gastroenterology. The UEG Research Prize was awarded to Prof Jesper Lagergren, for his paper titled "The aetiology, prevention and treatment of oesophageal cancer". Finally, the UEG Journal Best Paper Award was presented to Dr Clive H. Wilder-Smith, for his paper titled "Gastro-oesophageal reflux is common in oligo-symptomatic patients with dental erosion: A pH-impedance and endoscopic study."

Special attention was given to the UEG Week's 25th anniversary; attendees were given the opportunity to have their photo taken in a photo booth with their friends and colleagues, and to place their signature on an anniversary canvas to signify their attendance and participation. An additional celebration session was organised, at which attendees celebrated the major advances seen in digestive healthcare over the last 25 years. Discussion of these significant milestones was followed by attendees "looking into a crystal ball", predicting the future of digestive health medicine, the challenges which may arise, and how healthcare professionals and researchers can act to overcome these.

> "Just like previous years, I am extremely proud of our scientific programme, composed by the hardworking, scientific committee, and I am convinced that all of you will find many of our sessions to be of interest to you."

After these debates and discussions, Prof Manns invited all attendees to join him for a "surprise"; he completed his speech summarising the session, and Kool & The Gang's 'Celebration' began to play. Immediately, people gathered, forming an impressive human tower, and the pinnacle person revealed a banner featuring a golden '25' to the delight of the crowd.

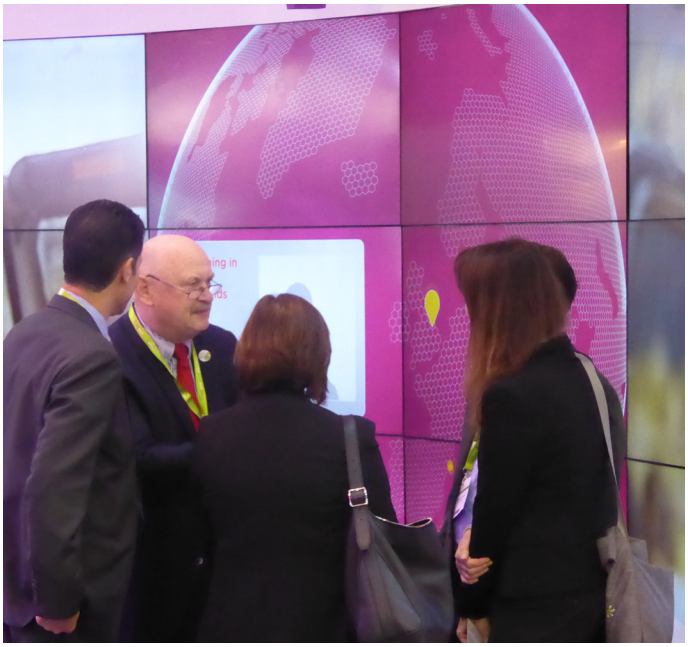
All of this and more provided all attendees with a wonderfully unique experience, which will be remembered for years to come. With continued expert opinion and participation, UEG Week really is a terrific event to attend with the aim of improving patient care. Here at EMJ we are already excitedly anticipating what is in store for next year's UEG Week, to be held in Vienna, Austria.

Long-Term Aspirin Use Reduces Risk of Digestive Cancers

ASPIRIN use over a long period of time has been shown to greatly reduce the incidence of cancers within the digestive tract, as well as in extragastric areas. Data presented at the 25th UEG Week, and reported in a UEG Week press release dated 31st October 2017, show that the number of digestive cancer cases was significantly higher in non-aspirin users than patients who were prescribed the painkiller for ≥6 months. Digestive cancers, including colorectal, gastric, and pancreatic, are responsible for nearly 25.0% of European cancer cases and 30.1% of all cancer-related deaths; therefore, the identification of a preventative therapeutic strategy is highly significant to the gastroenterology field.

A study, led by Prof Kelvin Tsoi, Chinese University of Hong Kong, Hong Kong, China, included >600,000 participants and evaluated the differences in cancer incidences between long-term aspirin users, with an average duration of aspirin prescription of 7.7 years, and those who were not prescribed the drug. As well as a reduction in the incidence of leukaemia, lung, and prostate cancers, there was a significant reduction in the number of cases of digestive cancers, including a vast reduction of 47% in the occurrence of both liver and oesophageal cancers. Gastric, pancreatic, and colorectal cancer incidences also decreased by 38%, 34%, and 24%, respectively, highlighting the substantial benefit of a long-term aspirin prescription to these patients.

> “What should be noted is the significance of the results for cancers within the digestive tract, where the reductions in cancer incidence were all very substantial, especially for liver and oesophageal cancer.”



Drawing conclusions from the results of prolonged aspirin use, Prof Tsoi commented: "What should be noted is the significance of the results for cancers within the digestive tract, where the reductions in cancer incidence were all very substantial, especially for liver and oesophageal cancer." The common pain relief medication, often used to treat an array of health conditions, has also recently been associated with protection against adverse cardiovascular events, leading clinicians to re-evaluate its usefulness in the medical community.

Research Calls for Earlier Colorectal Cancer Screening

RISING mortality rates in young adults suggest that colorectal cancer (CRC) screening should begin at the age of 45, according to new research from the Digestive Endoscopy Unit, Clinique de Paris-Bercy, Paris, France, presented at the 25th UEG Week and reported in a UEG Week press release dated 30th October 2017.

> "These findings demonstrate that it is at 45 years old that a remarkable increase in the colorectal lesions frequency is shown, especially in the detection rate of an early neoplasia."

A 400% increase in the detection of neoplasia was found in patients aged 45–49 years when compared to patients of a younger age, 40–44 years, after analysis of 6,027 colonoscopies. The 45–49-year-old group also exhibited an 8% increase in neoplasia rates compared to the 50–54-year-old cohort. The mean number of polyps and the detection rate of adenomas was also shown to increase by 95.8% and 95.4%, respectively, in patients aged 40–44 compared to patients aged 45–49 years old, respectively.

CRC is the second leading cause of cancer-related death in Europe, accounting for 215,000 European deaths every year, with 3 in 10 patients aged <55 years old. Screening for CRC has been demonstrated to reduce both incidence and mortality rates; however, inconsistencies in the CRC screening

schemes across Europe continue to fuel debate. Currently, the majority of screening programmes commence between 50 and 60 years of age.

Lead author, Dr David Karsenti, Clinique de Paris-Bercy, concludes that this research strongly suggests CRC screening should begin for patients at the age of 45, to facilitate the early detection and removal of polyps that may otherwise become malignant: "These findings demonstrate that it is at 45 years old that a remarkable increase in the colorectal lesions frequency is shown, especially in the detection rate of an early neoplasia."

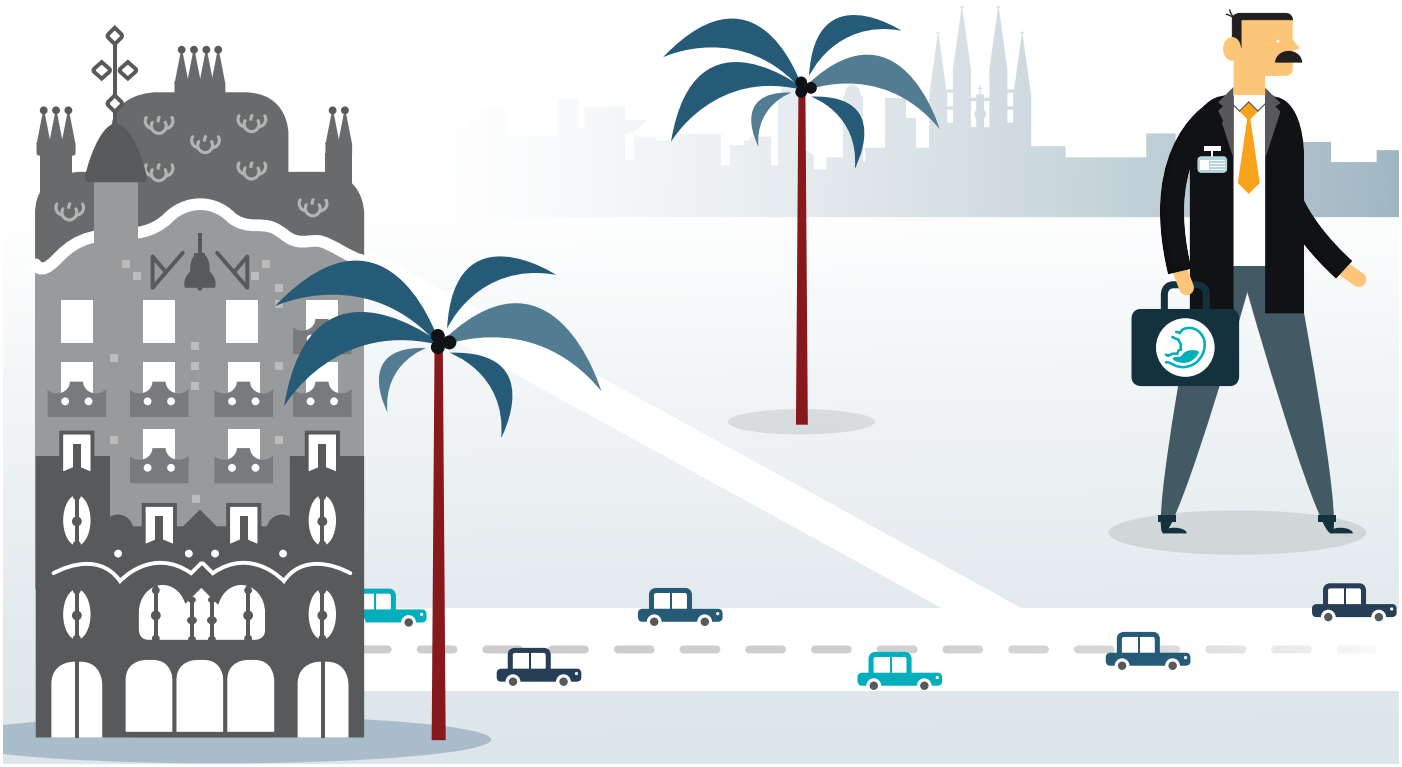
Crohn's Disease Symptoms Improved Within 1 Week of Ustekinumab Infusion

USTEKINUMAB, a drug already approved for the treatment of psoriatic arthritis, has been shown to improve symptoms within just 1 week of intravenous (IV) infusion in patients with moderately to severely active Crohn's disease, according to data reported in a UEG Week press release dated 30th October 2017.

> "These new results from the UNITI-1 trial are encouraging because they demonstrate that treatment with ustekinumab may begin to reduce patient-reported symptoms of Crohn's disease within just 1–2 weeks for a number of patients."

The exact cause of Crohn's disease is still unknown.[1] It is, however, known to be associated with immune system abnormalities and can be triggered by a genetic predisposition, diet, or environmental factors. Prof William Sandborn, University of California, San Diego, California, USA, commented that "The symptoms of Crohn's disease can cause significant distress to many patients, which is why it is important to find a treatment that can act rapidly to reduce the impact of the disease. These new results from the UNITI-1 trial are encouraging because they demonstrate that treatment with ustekinumab may begin to reduce patient-reported symptoms of Crohn's disease within just 1–2 weeks for a number of patients." There is currently no cure for Crohn's disease,[1] the need for an appropriate, effective, and fast-acting treatment of particularly severe symptoms is imperative to improve quality of life for Crohn's disease patients.

The UNITI-1 trial studied Crohn's disease patients who had previously been treated with tumour necrosis factor (TNF)-α antagonists but were either intolerant of the treatment or were unresponsive. Patients were treated with IV ustekinumab (130 mg or ~6 mg/kg), or placebo. Results were obtained through patient-reported outcomes using the Crohn's Disease Activity Index (CDAI), in which the following three symptoms were measured: daily frequency of loose stools, abdominal pain, and general wellbeing. CDAI data was collected from Week 0 to allow investigators to correctly identify the exact timeline of symptom improvement.



Results indicated that 19.6% and 17.6% of patients receiving ~6 mg/kg and 130 mg, respectively, had an improvement in symptoms within 7 days of IV ustekinumab infusion, including ≥50-point improvements in CDAI daily frequency of loose stools and abdominal pain. Significant symptom improvement was subsequently reported in 29.3% ($p<0.05$) and 31.4% ($p<0.01$) of those who received ~6 mg/kg and 130 mg, respectively, 14 days after IV infusion.

The UNITI-2 trail, comprised of patients who had gone through, and failed, conventional therapy but had not failed TNF-α antagonist treatment, were also treated with 130 mg or ~6 mg/kg IV ustekinumab, or placebo. This group was also found to have significantly higher clinical remission levels at Week 8 compared to placebo (~6 mg/kg $p<0.001$; 130 mg $p=0.009$).

A third trial, IM-UNITI, assessed the maintenance of response in patients who had or had not achieved clinical response 8 weeks after IV ustekinumab infusion from both the UNITI-1 and UNITI-2 trials. Patients were given a subcutaneous maintenance dose of 90 mg ustekinumab at Week 16. Data showed that, of the 219 patients who had not responded to the initial IV infusion, 37.6% and 60.5% from UNITI-1 and UNITI-2, respectively, had responded after the 90 mg subcutaneous maintenance dose.

Response and remission rates for patients receiving the initial IV dose of ~6 mg/kg in the UNITI-1 trial were 37.8% and 20.9%, respectively. These results increased to 47.4% and 24.1% after the 90 mg 16-week maintenance dose, respectively. Similar increases in response and remission results were also seen in the UNITI-2 trial group receiving ~6 mg/kg, Week 8 results after IV ustekinumab were 57.9% and 40.7%, respectively, and increased to 73.7% and 55.5%, respectively, after the 90 mg maintenance dose at Week 16.

Adverse reactions were mild and did not require cessation of treatment by any patients, the most common reactions reported were nasopharyngitis and headache. The most serious adverse reaction for ustekinumab reported has been hypersensitivity reactions including anaphylaxis.

These results are particularly encouraging, especially with regard to the rapid effect the IV ustekinumab had on patient symptoms. Relieving some of the most distressing symptoms of Crohn's disease will no doubt improve the quality of life experienced by Crohn's disease patients. Currently, the use of ustekinumab for the treatment of Crohn's disease is approved in 40 countries around the world; however, ustekinumab's approval for other diseases including sever plaque psoriasis and psoriatic arthritis is more than

double that for the treatment on Crohn's disease. With the help of such promising data from trials such as these, will hopefully accelerate the approval for ustekinumab for the treatment of Crohn's disease in even more countries.

REFERENCES

1. Crohn's and Colitis UK. Crohn's disease. Available at: http://www.crohnsandcolitis.org.uk/about-inflammatory-bowel-disease/crohns-disease. Last accessed: 06 November 2017.

Risk of Gastric Cancer Reduced Following *Helicobacter Pylori* Treatment

ELIMINATION of the *Helicobacter pylori* carcinogen from the stomach can reduce the risk of gastric cancer, particularly in older populations, according to study results presented at the opening plenary session of the 25th UEG Week. As the fourth biggest contributor to cancer-related deaths in the world and with a high incidence of diagnosis in patients with an average age of 69 years, the discovery of new preventative treatment modalities for gastric cancer is essential in this vulnerable population.

The data, reported in a UEG Week press release dated 31st October 2017, summarised research on the consequences of antibiotic therapy for *H. pylori* infection in the elderly. Using a population-based study involving >63,000 people, Prof Wai Keung Leung, Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong, and his team highlighted the differences between gastric cancer incidence following antibiotic treatment in elderly participants and the general population. Of those patients aged >60 years who received antibiotic treatment for an *H. pylori* infection, 0.8% developed gastric cancer, compared to 1.1% of age-matched patients from the general population; this observation equated to a 22% reduction in the risk of stomach cancer in elderly patients following eradication of the pathogen.

> "...we can now confidently recommend that the *H. pylori* infection should be treated in the elderly to help reduce their risk of developing gastric cancer."

The *H. pylori* infection is believed to affect >50% of the world's population; however, the majority of cases are only diagnosed following onset of symptoms, including gastric irritation. These findings highlight the importance of diagnosing and treating *H. pylori* infections in older patients at a significant risk of developing gastric cancer because the pathogen, which inhabits the stomach lining, has been shown to contribute to 78% of all global gastric cancer cases.

Commenting on the significance of the study results, Prof Leung described the reduction in gastric cancer incidence in elderly patients as "remarkable" and suggested that treatment of the *H. pylori* infection is of great value to this population. He added: "Although it has been commonly thought that it may be too late to give *H. pylori* eradication therapy to older subjects, we can now confidently recommend that the *H. pylori* infection should be treated in the elderly to help reduce their risk of developing gastric cancer."

Patients with Obesity Are Not Receiving Adequate Care

OBESE patients are facing a multitude of barriers to successful treatment according to a press release from UEG Week 2017.

The awareness, care, and treatment in obesity management (ACTION) study investigated barriers in obesity management from the perspective of people with obesity, healthcare professionals, and employers nationwide in the USA. The aim of the study was to generate insights to guide collaborative action to improve obesity care, education, and support. In total, 3,000 people with obesity, 600 healthcare professionals, and 150 employers were included in the study.

Obesity can be influenced by physiological, psychological, genetic, and socio-economic factors and requires long-term management. There are many, serious obesity comorbidities including Type 2 diabetes mellitus, heart disease, and some cancers; perhaps the most serious consequence of obesity is a shortened life expectancy when compared to those of a healthy weight.

The ACTION study presented results indicating that very few of the >90 million Americans with obesity are seeking or receiving long-term obesity care. One of the statistics presented showed that, of the 71% of obese people who had spoken to a healthcare professional about their weight in the last 5 years, only 55% reported having a diagnosis of obesity and as little as 24% were offered follow-up care.

Five key barriers to comprehensive obesity care were identified by the ACTION study from obese patients themselves, healthcare professionals, and employers:

- Only a small number of obese people who start weight loss attempts are able to maintain the achieved weight loss
- Most people with obesity believe weight loss is their personal responsibility, preventing them from seeking help, despite obesity now being recognised as a disease
- Almost half of obese people have not been given an obesity diagnosis
- Dialogue about weight management is insufficient with patient-provider and has limited follow-up
- Employer wellness programmes are insufficient at meeting the needs of people with obesity

"The barriers identified in the study highlight opportunities to bridge gaps in understanding to facilitate true collaboration among all stakeholders" commented co-author Dr Angela Golden, Nurse Practitioner, Munds Park, Arizona, USA. "Only by bridging these gaps will obesity care become integral to standard practice, whether in the healthcare or employment setting, and people with obesity will have the care and support needed to effectively treat their obesity."

"We in the healthcare community must ask why this epidemic is not being diagnosed and treated with the same urgency and focus as any other serious diseases?" said Dr Lee Kaplan, Massachusetts General Hospital, Boston, Massachusetts, USA. Dr Kaplan went on to say "We need to fundamentally rethink obesity so that the public and healthcare community understand more about the biology, chronicity, and overall health impact of this disease. Real progress can be achieved if we can overcome the entrenched mindsets that generate the barriers revealed by this study."

"The barriers identified in the study highlight opportunities to bridge gaps in understanding to facilitate true collaboration among all stakeholders..."

Colorectal Cancer Diagnosis: The Future is Artificial Intelligence

ARTIFICIAL INTELLIGENCE (AI)-assisted endoscopy has previously demonstrated success in the classification of colorectal polyps in preliminary studies; now, in one of the first prospective trials using this technology, colorectal adenomas have been successfully identified automatically, a UEG Week press release dated 30th October 2017 reported. Speaking about the findings of the trial, the lead study author, Dr Yuichi Mori, Showa University, Yokohama, Japan, announced: "The most remarkable breakthrough with this system is that AI enables real-time optical biopsy of colorectal polyps during colonoscopy, regardless of the endoscopist's skill." Dr Mori went on to discuss how being able to distinguish adenomas in real-time would facilitate the complete resection of any neoplastic lesions, and noted: "This is thought to decrease the risk of colorectal cancer and, ultimately, cancer-related death."

The AI-assisted endocytoscopy diagnostic system uses a 500-fold magnification of a colorectal polyp to assess ~300 of its features; this is achieved by utilising the narrow-band imaging mode or staining with methylene blue. These features are then compared to >30,000 endocytoscopic images previously learned by the machine; this enables a prediction of polyp pathology in less than a second.

The prospective study involved 250 men and women, all of whom had previously been diagnosed with colorectal polyps, identified through endocytoscopy. A pathological report, produced after the surgical removal of polyps specimens, was used to compare results to the predicted pathology obtained by the AI-assisted system, which analysed a total of 306 polyps in real-time. This comparison showed the system to have a 94% sensitivity, 79% specificity, and 86% accuracy; the positive and negative predictive values were 79% and 93%, respectively.

These findings suggest that use of this system could enable successful removal of cancerous polyps whilst preventing unnecessary removal of polyps that may be non-neoplastic, greatly improving upon the current stagnating clinical procedures. Dr Mori explained: "We believe these results are acceptable for clinical application and our immediate goal is to obtain regulatory approval for the diagnostic system." The research team are now undertaking trials to achieve this whilst also developing an automatic polyp detection system.

> "This is thought to decrease the risk of colorectal cancer and, ultimately, cancer-related death."

Study Confirms Efficacy of Radiofrequency Treatment for Pancreatic Cancer

ENDOSCOPIC ultrasound (EUS)-guided radiofrequency (RFA) is a feasible treatment for pancreatic neuroendocrine tumour (PNET) and pre-malignant intraductal pancreatic mucinous tumour (IPMN) with a low rate of complications, according to trial results presented at UEG Week 2017.

Following several positive studies of the procedure, a French prospective multicentre trial was initiated by Dr Marc Giovannini, Institut Paoli Calmettes, Marseilles, France, to further test the efficacy of this treatment in pancreatic tumours. The study, which spanned from September 2015–September 2016, included 30 patients who were not operable or who had refused surgery. There were 16 males and 14 females, and the mean age was 55.4 years (range: 49–84 years). Of the 30 patients, 18 had cystic tumours, 17 of whom suffered IPMN, and 12 had a PNET.

> “...EUS-guided treatment with RFA is feasible with a low rate of pancreatitis and complications...”

For the procedure, the generator setting was 50 watts and an electrical impedance 100 Ohms. Using an 18G needle, with the active part 10 mm in length, the procedure was stopped when white bubbles appeared, or when the impedance reached >100 Ohms. The aim was for the radiofrequency to destroy the cells by heat and for the destruction of the cells to induce an immunomodulation and secretion of the cytokines and lymphocyte killers, causing an anti-tumour effect on the lesion. During his presentation, Dr Giovannini proceeded to show images of lesion ablation in several patients included in the study. In the case of the PNET displayed, the procedure was successfully completed in a matter of seconds; for IPMN, it took a little longer, with two or three shots of radio frequency required to totally ablate the lesion.

At 6-month follow-up of PNET patients, there was a significant response rate of 82% and 7 participants had either complete necrosis or disappearance of the tumour. At 12-month follow-up, no recurrence occurred in these 7 patients. In regard to IPMN, 13 of the 17 patients were followed for at least 6 months; at this stage, the significant response rate was 69%, with 7 participants achieving complete resolutions, 2 having a reduction in tumour diameter of >50%, and 3 with no response. After 12 months, there was one further complete response. There were three complications in the study (1 mild pancreatitis, 1 delayed perforation, 1 pancreatic duct stenosis); the pancreatitis and delayed perforation occurred during the first two procedures. Following changes in the protocol study to address this, the complication rate was reduced to just 3.5%.

“To conclude, EUS-guided treatment with RFA is feasible with a low rate of pancreatitis and complications,” commented Dr Giovannini. “EUS-guided RFA can induce a complete and partial response of a PNET of <2 cm in 75% of cases, and of an IPMN, in 70%. Of course, we need to follow these patients to evaluate the duration and outcome of this response.”

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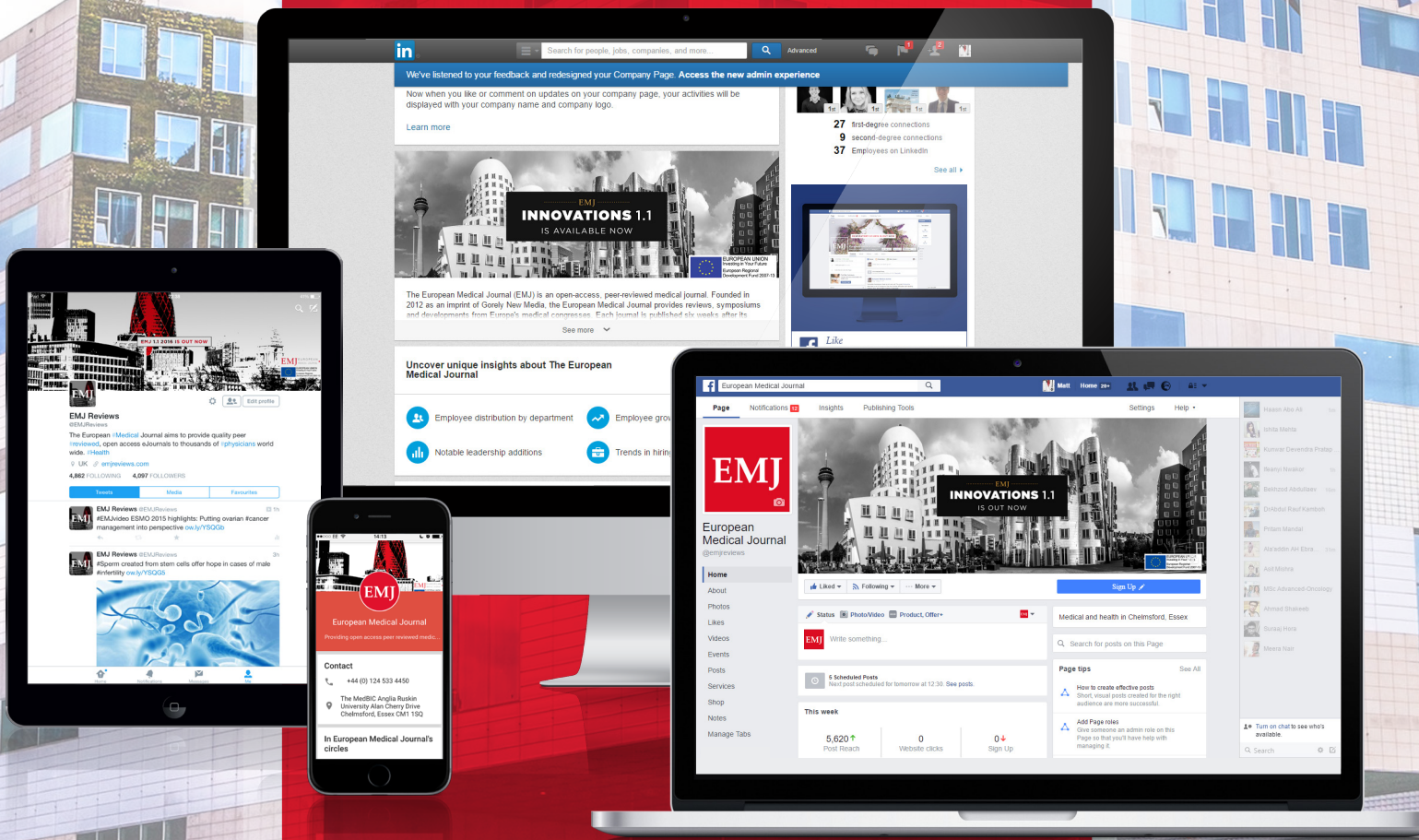

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Davor Štimac

Head of Gastroenterology, Internal Clinic Department, University Hospital Rijeka, Rijeka, Croatia; President of the Croatian Pancreatic Club, and President of the Croatian Society of Obesity; Member of the European Board of Gastroenterology.

Q: Firstly, could you tell us about what first inspired you to specialise in gastroenterology?

A: I was inspired mostly by the make-up of gastroenterology, as a part of internal medicine with a lot of theoretical knowledge, as well as including endoscopy as an invasive and practical method.

Q: You are involved in a variety of medical associations, including the Croatian Pancreatic Club. Could you tell us a little about your role as President and how associations such as this impact research and collaboration in the scientific community?

A: I started my clinical work in the field of pancreatology, particularly acute pancreatitis, and through years with my team, I have published a lot of high quality papers in that field. Our group attended many conferences in Croatia and other countries, and eventually we formed a Croatian Pancreatic Club. I was a member of the abstract selecting committee for the European Pancreatic Club for 4 years. At the moment, the Croatian Pancreatic Club is collaborating with the European Pancreatic Club as its mother organisation in many fields, but mostly education of the younger members. We are part of the Croatian Gastroenterology Association and we are participating in many conferences, initiatives, and projects, mostly associated with education and scientific presentations.

Q: You are also affiliated with a number of educational institutions, including your role as Professor at the School of Medicine, University of Rijeka, Rijeka, Croatia, the same school that you graduated from. What teaching role do you perform at this institution, and what do you enjoy most about being involved in the progression of young medical students?

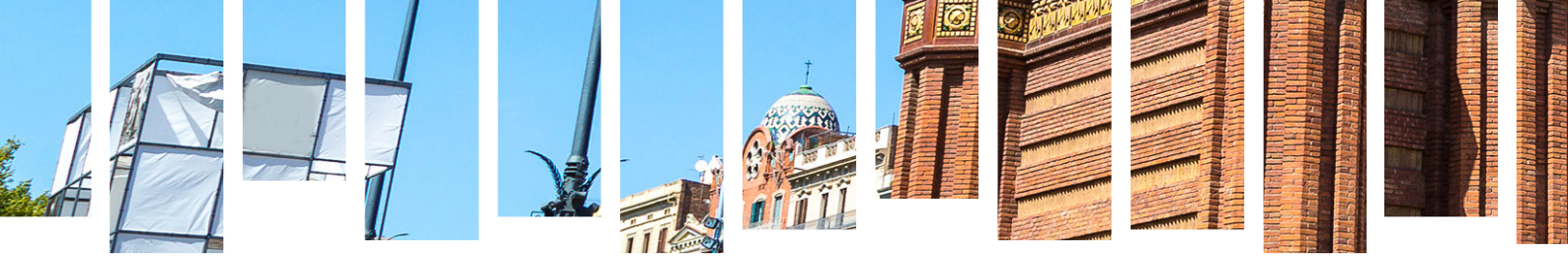
> “Pancreatic cancer is still an almost non-curative disease...”

A: In Croatia, many professors have the opportunity to work in the institutions where they graduated. This is connected to our tradition of low mobility inside our small country, with only four Schools of Medicine in Croatia. As a teacher, I am educating medical and dentistry students, but also nurses and nutritionists. In addition, I am a lecturer in teaching programmes for gastroenterologists, management, and evidence-based medicine. In the field of gastroenterology, I am teaching PhD students and as well as lecturing and working with them on their PhD theses. Teaching and mentoring young people is crucial for progression in medicine.

Q: We understand you have a special interest in pancreatic disease. With the incidence of pancreatic cancer increasing year-on-year and the 10-year survival rate measuring <1%, what do you believe is hindering survival rates of pancreatic cancer patients compared to other cancers?

A: Pancreatic cancer is still an almost non-curative disease, with a very low percentage of patients surviving past 1, 5, or 10 years. New drugs are prolonging survival for weeks or months, but very rarely for years. This is compared with other gastrointestinal tumours and we are still looking for more potent drugs for better treatments. Pancreatic cancer is usually diagnosed too late because, during the phase when it is operable, it is asymptomatic in most of the patients.

Q: You have published a number of papers on the prevention of pancreatitis, both as an acute and chronic life-threatening condition; what advances have been made in the prevention of pancreatitis in recent years?



> I am expecting major advances in the field of gastro-oncology, with many new personalised drugs being developed.

A: Prevention of acute pancreatitis is mostly connected with prevention of alcohol abuse and gallstone disease since these are the two main causes of the disease. Obesity, food intake, and metabolic syndrome have connections with gallstones. Acute pancreatitis is mostly preventable and knowledge about its aetiology can save many patients from hospitalisations.

Q: You also have an interest in endoscopy techniques, and have published a paper this year detailing the emerging technologies and challenges of bariatric endoscopy. What were the take-home messages from this paper and what do you believe it has added to the field of gastroenterology?

A: Bariatric endoscopy is a treatment that can help patients who are resistant to dietetic measures and medicament therapies, but also it can be an aid to surgery in patients with extreme obesity. Many new endoscopic techniques are developing in the field of obesity treatment, but most of them display doubtful results.

Q: As a previous speaker at a number of international meetings, what role do you believe international congresses, such as the United European Gastroenterology Week (UEGW), play in the collaboration and progression of science?

A: UEGW is currently one of the most prestigious congresses in gastroenterology. It covers all the fields and topics in gastroenterology and with parallel sessions, interactive programmes, practical workshops, and many other events, it gathers almost 15,000 gastroenterologists, mostly from Europe but also from all over the world. Scientific, educational, and public affairs committees of UEGW take great care when preparing UEGW, resulting in the development of an event where professional and scientific exchange is at its highest level. Collaboration between young gastroenterologists and top experts within the field, exchange of Eastern and Western world experience, and debates between gastroenterologists and digestive surgeons also play a part in this meeting.

Q: During the next 5 years, is there a specific challenge within the gastroenterology field that you would like to be addressed and resolved?

A: New and expensive drugs with the potential to cure the hepatitis C epidemic are a big challenge for hepatologists. In the next 5 years this problem could be resolved, but it is highly dependent on drug prices.

Q: Like many scientific fields, gastroenterology is ever-evolving. What do you anticipate being the major advances made in the field in the coming years?

A: I am expecting major advances in the field of gastro-oncology, with many new personalised drugs being developed.

Q: Finally, do you have any advice for a budding gastroenterologist hoping to pursue a career in this therapeutic area?

A: Gastroenterologists have the potential for a successful career because there are many, very different and specific, parts of gastroenterology with challenging diagnostic and therapeutic possibilities. For a career in gastroenterology, it is necessary to connect scientific knowledge from basic science with clinical practice. Samples of tissue necessary for clinical investigation are easily available from any part of the gastrointestinal tract, without surgical intervention. Motivated young doctors who select a career in gastroenterology have a good chance for an academic career.

> Scientific, educational, and public affairs committees of UEGW take great care when preparing UEGW, resulting in the development of a place where professional and scientific exchange is at its highest level.

Venkata Pawan Kumar Lekharaju

Consultant Gastroenterologist and Physician, Wirral University Teaching Hospital NHS Trust, Upton, UK.

Q: Firstly, could you begin by giving us an insight into what encouraged you to pursue a career in gastroenterology? Was there a specific event or person that inspired you?

A: I was always interested in performing procedures and was very keen to pursue a career in a surgical speciality; however, the nature of a physician's job, which involves a thorough understanding of the basics, also interested me; thus, I became a physician. I then chose the specialty of gastroenterology, which enabled me to perform procedures and also be able to enjoy being a physician.

Q: You work as a consultant gastroenterologist and physician at the Wirral University Teaching Hospital NHS Trust. What are your day-to-day roles and responsibilities at the hospital?

A: I work in a team of 10 gastroenterologists, 2 registrars, 3 junior doctors, and 9 specialist nurses. My day-to-day role includes performing endoscopic procedures. I do four lists a week (endoscopic retrograde cholangio-pancreatography, endoscopic ultrasound (EUS), colonoscopy, and therapeutic endoscopy). I also attend two outpatient clinics. I do ward rounds and provide an opinion on hepato-pancreato-biliary cases referred to me mainly from surgical specialists.

Q: As a consultant, you get to see the direct effect that advances in research can have on patient treatment. What do you believe has been the biggest advance in the field of gastroenterology during your career?

A: Many areas of gastroenterology have seen important advances during my career.

For endoscopy, single-operator cholangioscopy, lumen-apposing metal stents, and interventional EUS have all been influential. For hepatology, Fibroscan®, a non-invasive alternative to liver biopsy, has been important for the treatment for hepatitis C infection. For irritable bowel disease, anti-tumour necrosis factor treatment has made a large impact, as have surveillance techniques for colorectal cancer.

Q: What do you think is needed to further advance the field? What milestones would you like to see achieved in the next 5 years?

A: I would like to see the cost of effective drugs and endoscopic accessories lowered, so that the best treatment is within the reach of everybody, regardless of income.

Q: Is there any condition which you feel is undeservedly lacking in research?

A: Alcoholic liver disease.

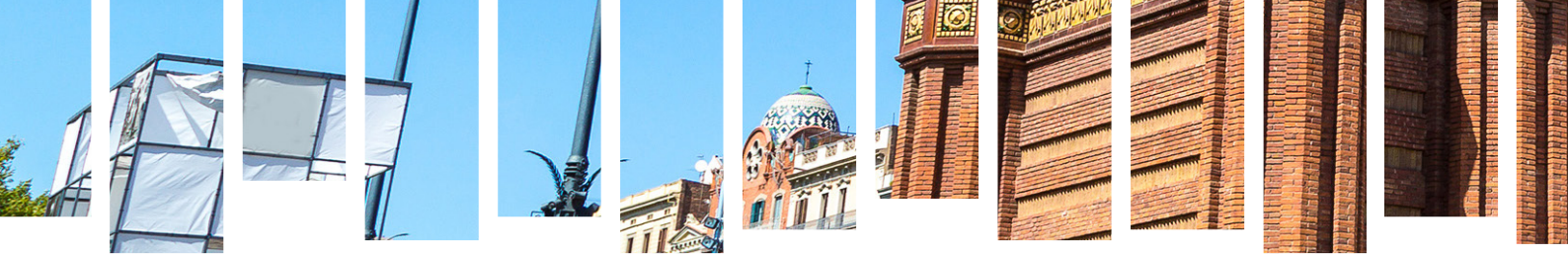
Q: The NHS is under increasing pressure, with many financial cuts being enforced in recent years. What effect do you think implementing such severe cuts to the public health service will have on your day-to-day practice?

A: The care provided will be compromised and the standard of care will decline.

Q: You wrote a paper as part of a Therapeutic Endoscopic Retrograde Cholangiopancreatography (ERCP) update from the United European Gastroenterology Week (UEGW) 2013, showing that cholangioscopy-assisted electrohydraulic lithotripsy is highly effective in the management of difficult bile duct stones. What do you think this update has brought to the field?

A: Better management of patients with difficult common bile duct stones.

> "Empathy and patient-centred care should be a major focus for the upcoming generation."



Q: A recent study presented at the 2016 meeting of the New York Society for Gastrointestinal Endoscopy, discussed the relatively poor quality of online content relating to irritable bowel disease and ulcerative colitis. With more people than ever before consulting the internet for medical advice, what impact does this have on your medical practice?

A: This can lead to difficult consultations with the patients in the clinic. Patients come with preconceived notions about their symptoms and fail to trust the scientific knowledge and experience of a senior consultant.

Q: What has been your proudest moment as a gastroenterologist?

A: Seeing the happy faces of the patients with complex diseases following a curative or effective treatment.

Q: Finally, what aspects of the field do you think should be the focus of the next-generation of gastroenterologists?

A: Empathy and patient-centred care should be a major focus for the upcoming generation.

> “I would like to see the cost of effective drugs and endoscopic accessories lowered, so that the best treatment is within the reach of everybody, regardless of income.”

Waseem Hamoudi

Consultant of Gastroenterology & Hepatology, Royal Hospital, Amman, Jordan; Secretary General of the Jordanian Society of Gastroenterology & Hepatology (2008-2017), Member and Examiner of the Jordanian Board of Gastroenterology (2010-2017).

Q: What was it that first inspired you to specialise in the field of gastroenterology?

A: During my residency for general internal medicine from 1991–1994, I had a patient with chronic debilitating diarrhoea with hypokalaemia that was fully investigated to find a cause of this disease. We did not find a cause of her symptoms until she underwent upper endoscopy with push enteroscopy, which revealed a small intestinal (jejunal) mass; it was my first time seeing upper endoscopy carried out by my mentor, Prof Ovidiu Pascu in Cluj Napoca, Romania. This event inspired me to specialise in gastroenterology.

> “The financial burden of the new treatments for chronic digestive illnesses is a big problem that we are facing now...”

Q: Could you provide us with a glimpse into your roles and responsibilities as a Consultant of Gastroenterology and Hepatology, Royal Hospital, Amman, Jordan?

A: I am now a consultant in the private sector after 22 years serving the public and academic sector, specialising in the field of gastroenterology and hepatology in various countries, such as Romania, Netherlands, Japan, and Jordan. I have been head of the gastroenterology and hepatology specialty at the Ministry of Health in Jordan since 2010 and head of the Internal Medicine department at Al Bashir Teaching Hospital since 2012. I am also a Clinical Associate Professor at Jordan University Hospital for the speciality of internal medicine, teaching and developing the field of gastroenterology and hepatology practice with my gastroenterologist colleagues in Jordan.

Q: Jordan has seen much development in the practice of gastroenterology over the years. Could you provide us with some more information on the history of and advancements made in gastroenterology in this country?

A: The first endoscopy procedure in Jordan was carried out in 1973 by Prof M Shonaq, and since that time endoscopy was carried out only in teaching and public hospitals, until the end of the 1970s when the use of endoscopy for diagnostic and therapeutic procedures was carried out also in private hospitals. In the mid-1980s, the Jordanian Board of Gastroenterology was created in order to regulate the profession of gastroenterology. Since 1985, the Jordanian Board of Gastroenterology has been recognised in the Middle East and the Gulf as the qualifying board for practicing the speciality of gastroenterology in this area.

Q: Following this, is there anything particularly distinct about the practice of gastroenterology or the challenges faced by gastroenterologists in Jordan compared to other countries?

A: The practice of gastroenterology and hepatology in Jordan is strictly regulated and governed by the Jordan Medical Association (JMA) under the direct supervision and control of the Jordanian Society of Gastroenterology and Hepatology, which was established in 1988 and aims to improve the practice, research, and organising framework and guidelines in the field of gastroenterology and hepatology in Jordan. The Jordanian Society for Gastroenterology and Hepatology is a forum for the exchange of ideas in gastroenterology and hepatology, particularly through promotion of postgraduate education, research, and training. This was achieved by collaboration with different governmental and non-governmental institutions for the improvement of medical practice in the field of gastroenterology and hepatology. In addition, the forum stimulates investigation for research in the field, forming consensus algorithms for different issues and for the best evidence-based updated medical practice and organisation of postgraduate courses and congresses with an emphasis on clinical gastroenterology and hepatology. Collaboration with international organisations of gastroenterology, such as the World Gastroenterology Organisation (WGO), the European Society of Gastrointestinal Endoscopy (ESGE), and others, was an early aim of the society, in order to apply and maintain the international standards for practicing the speciality in Jordan.

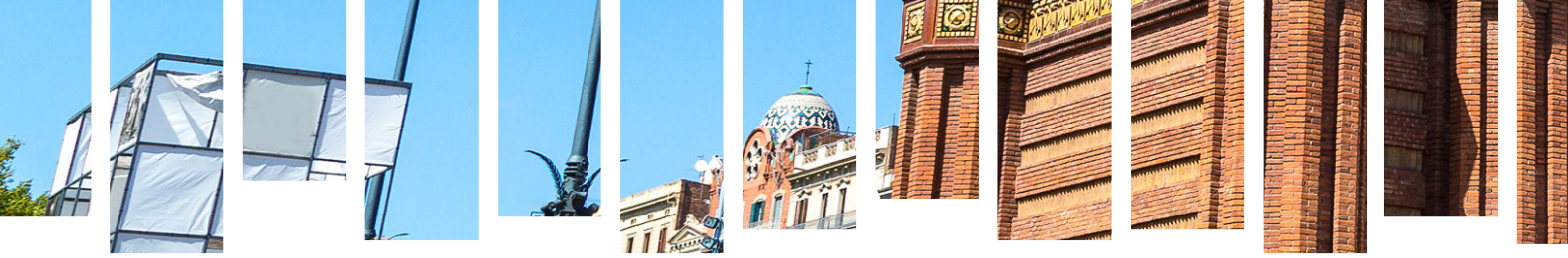
Q: Since the start of your career, what discoveries do you consider to have been the most significant within the field of gastroenterology?

A: The introduction of endoscopic retrograde cholangiopancreatography in the 1970s was a big step in therapeutic endoscopy. Also, the progress of therapeutic endoscopy, including endoscopic mucosal resection and endoscopic submucosal dissection, made the specialty of gastroenterology a major contributor in the field of digestive surgery and oncology.

Q: How important are events such as the annual United European Gastroenterology Week (UEGW) congress to gastroenterologists? Is there anything in particular that you hope to take away from events such as this?

A: Our geographical area of the world is considered as a developing area in all aspects of life, including the medical sector, and surely the need to follow new developments and techniques in gastroenterology, and meet with world-recognised pioneers and researchers, exchanging and gaining experience, is vital. Europe is a neighbouring continent for the Middle East and is generally easy to reach for the physicians from our region. The UEGW is known as a major event that includes world-recognised experts in the field of gastroenterology who share their experience with other colleagues, so it is not a surprise that it gathers lots of young and experienced gastroenterologists from our region and is frequently attended by them.

> “My advice is do not hesitate to do what you can do, do not be afraid of mistakes, learn from your faults, and improve yourself.”



Q: You recently wrote on the topic of irritable bowel syndrome (IBS) in Jordan and spoke about a plan to perform a nationwide statistical analytical study to investigate the prevalence of IBS. The study will be conducted in association with the Jordanian Society of Gastroenterology and Hepatology, of which you are Secretary General. Can you provide us with any further details about the study and its context?

A: One of the main aims of the Jordanian Society of Gastroenterology and Hepatology is to stimulate investigation and research in the field of gastroenterology and hepatology, and in 2016 we promoted a survey that includes Jordanian gastroenterologists from various medical sectors, including public and private, to try to have a nationwide statistical study regarding the prevalence of IBS in Jordan. I think it will commence and be published next year.

Q: In addition to your everyday responsibilities as a consultant, you are involved in a number of other activities, such as being Secretary General of the Jordanian Society of Gastroenterology and Hepatology, an examiner and member of the Jordanian Board of Gastroenterology, and authoring the chapter 'Endoscopic Retrograde Cholangiopancreatography (ERCP)' for Hepatogastroenterology, Part II: Gastroenterology. As a doctor, do you feel it is important to be involved in additional activities beyond research and clinical work?

A: I think that one of our responsibilities as physicians is to teach and stimulate other young physicians in continuing the development and research in the field of gastroenterology and hepatology and to establish a strong foundation of the specialty that others can continue to build and improve upon in co-operation with colleagues from other countries, with the ultimate aim of helping our patients and easing their suffering. Humanitarian and charitable work is also important for every physician, in order to keep in touch with our suffering brothers and sisters worldwide.

Q: In your opinion, what do you think the biggest challenges and obstacles will be for gastroenterologists in the next 5 years?

A: The financial burden of the new treatments for chronic digestive illnesses is a big problem that we are facing now and I think it will be a problem in the future (for example biologic therapies, Direct Antiviral Agents, and others). We should think about how to make those treatments available for all patients, involving pharmaceutical companies, medical insurance, and non-governmental organisations in order to facilitate access to them.

Q: If you could go back in time and give your younger self one piece of professional advice, what would it be?

A: It is very difficult to assume that if you go back in time you could prevent a mistake or a certain pathway that you followed because all of your knowledge is a combination of mistakes and solutions for those mistakes. My advice is do not hesitate to do what you can do, do not be afraid of mistakes, learn from your faults, and improve yourself.

> "I think that one of our responsibilities as physicians is to teach and stimulate other young physicians in continuing the development and research in the field of gastroenterology and hepatology..."

KEEP CALM AND TREAT TO TARGET IN INFLAMMATORY BOWEL DISEASE

This symposium took place on 30th October 2017, as part of the 25th United European Gastroenterology (UEG) Week in Barcelona, Spain

Chairperson

Jean-Frédéric Colombel[1]

Speakers

Jean-Frédéric Colombel,[1] Benjamin Pariente,[2] Geert D'Haens[3]

1. Icahn School of Medicine at Mount Sinai, New York City, New York, USA

2. Gastroenterology Department, Claude Huriez Hospital, University of Lille, Lille, France

3. Academic Medical Centre, Amsterdam, Netherlands

Disclosure: Prof Colombel has acted as a consultant or advisory board member for AbbVie, ABScience, Amgen, Bristol-Myers Squibb, Celltrion, Danone, Ferring, Genentech, Giuliani SPA, Given Imaging, Janssen, Immune Pharmaceuticals, Medimmune, Merck & Co, Millenium Pharmaceuticals Inc, Neovacs, Nutrition Science Partners Ltd, Pfizer Inc, Prometheus Laboratories, Protagonist, Receptos, Sanofi, Schering Plough Corporation, Second Genome, Shire, Takeda, Teva Pharmaceuticals, Tigenix, UCB Pharma, Vertex, and Dr August Wolff GmbH & Co.; and a speaker for AbbVie, Falk, Ferring, Janssen, Merck & Co, Nutrition Science Partners Ltd, Takeda. Dr Pariente has received consulting fees from AbbVie, MSD, Ferring, Takeda, Janssen, Bioagaran, and Pfizer. Prof D'Haens has acted as an advisor for AbbVie, Ablynx, Amakem, Amgen, AM-Pharma, Avaxia, Biogen, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene/Receptos, Celltrion, Cosmo, Covidien/Medtronic, Ferring, DrFALK Pharma, Eli Lilly, Engene, Galapagos, Genentech/Roche, Gilead, GlaxoSmithKline, Immunic, Johnson & Johnson, Lycera, Medimetrics, Millenium/Takeda, Mitsubishi Pharma, Merck Sharp Dohme, Mundipharma, Nextbiotics, Novo Nordisk, Otsuka, Pfizer/Hospira, Prometheus laboratories/Nestlé, Protagonist, Robarts Clinical Trials, Salix, Samsung Bioepis, Sandoz, SetPoint, Shire, Teva, TiGenix, Tillotts, Topivert, Versant, and Vifor; and has received speaker fees from AbbVie, Biogen, Ferring, Johnson & Johnson, Merck Sharp Dohme, Mundipharma, Norgine, Pfizer, Samsung Bioepis, Shire, Millenium/Takeda, Tillotts, and Vifor.

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MEETING SUMMARY

The goal of this symposium was to highlight the importance of early diagnosis, assessing prognostic factors, and treating to target in inflammatory bowel disease (IBD). In the introduction, Prof Colombel outlined the treat to target (T2T) and tight control (TC) approach, which involves predefining treatment targets in consultation with patients, continuously monitoring disease activity, and modifying treatments until targets are achieved. Dr Pariente presented regarding the progressiveness of Crohn's disease (CD) and described the Lémann index (LI), which assesses cumulative structural damage in CD.[1] He outlined the 'window of opportunity' in early disease, within which disease progression could be stopped. Dr Pariente said the T2T approach presents the opportunity for a personalised method of treatment; if targets are not achieved, treatment is intensified or switched. Prof Colombel presented the results of the CALM study,[2] in which CD patients were randomised 1:1 to clinical management (CM) or TC, meaning treatment was escalated based on clinical symptoms in combination with biomarkers. The primary endpoint of mucosal healing and no deep ulceration was achieved by 45.9% of patients in the TC arm versus 30.3% in the CM arm (p=0.010). Lastly, Prof D'Haens presented a cost-effectiveness analysis using data from CALM. The calculated total direct medical costs for the TC arm were £13,296 versus £12,627 for the CM arm (a direct medical cost difference of £669).[3] The quality-adjusted life years (QALY) were 0.684 for the TC arm

versus 0.652 for the CM arm (giving a QALY difference of 0.032). The incremental cost-effectiveness ratio showed a cost of £20,913 per QALY gained, which falls within the threshold of The National Institute for Health and Care Excellence (NICE) guidance for cost-effectiveness.

Introduction: Where Are We in 2017?

Professor Jean-Frédéric Colombel

Although progress has been made in the study of IBD, particularly regarding biologics, studies demonstrate treatment gaps and unmet needs. In the past, CD was considered intermittent with flares and remissions; however, gastroenterologists have come to appreciate that it is a progressive disease with the possibility that each flare could result in bowel damage. Studies suggest that damage and disability scores increase from diagnosis (with patients experiencing stricture, fistula or abscess, and surgery) while inflammatory activity (measured by Crohn's disease activity index [CDAI], Crohn's disease endoscopic index of severity [CDEIS], and C-reactive protein [CRP]) fluctuates.[1]

The LI, a score of bowel damage including location, severity, extent, progression, and reversibility, has changed the disease paradigm. The index, developed by the International Program to Develop New Indexes in Crohn's Disease (IPNIC), demonstrates that each flare leads to bowel damage (strictures, fistulas, abscesses, and surgery).[1] Additionally, there are data suggesting ulcerative colitis (UC) is progressive, starting with proctitis, leading to left-sided colitis and extending to pancolitis (the most difficult condition to treat).[4]

The current goal of CD management is to control progression, leading to the window of opportunity concept whereby if treatment is missed in the subclinical period, the condition will progress. Although IBD management has evolved, the current clinical goal is to obtain sustained remission and reduce steroid use. The new target is endoscopic healing, associated with steroid-free remission, decreased hospitalisations, decreased surgery, and improved quality of life. Future targets are likely to move beyond deep remission (endoscopy findings) to transmural healing, reducing and preventing intestinal damage, which may in turn reduce or prevent disability.[5-7]

The aim of T2T is to avoid development of serious complications and disability.[8] The concept involves treating to predefined treatment targets associated with optimal long-term outcomes (goal-orientated approach), and regular monitoring of the target and/or surrogate marker with optimisation of treatment when targets are not met. Additional principles include tailoring treatment, monitoring individuals, and de-escalating therapy when goals are achieved, if suitable. For success, it is important to involve patients, identify T2T targets together, continuously monitor disease activity, and modify treatment until targets are reached.[6-8]

In Focus: Importance of Early Diagnosis and Treating to Target in Inflammatory Bowel Disease

Doctor Benjamin Pariente

To understand the importance of applying T2T strategies, there is first a need to consider why IBD patients should be treated as early as possible. While CD and UC are known to be chronic progressive diseases, current indexes only assess inflammatory activity (whether clinical, endoscopic, or biological). Such indexes often have the same values for different patients with early or longer term CD, indicating the need for indexes and tools to capture progression and damage.

Recognition of such requirements led to the development of two new indexes: the first disability index for IBD, and the first digestive damage index in CD, named the LI,[1,9-12] which assesses cumulative structural damage in CD. In the LI, the gastrointestinal tract is divided into four regions, each of which is subdivided into serial segments. For each segment, strictures, penetrating lesions, and previous surgery can be scored on a scale with four levels (from null to severe) according to severity, providing an overall index score that can be used to assess damage progression, evaluate treatment, and provide an endpoint for trials.

A study assessing digestive tract damage in 138 CD patients (median age: 34 years) showed that damage was related to disease duration; the LI was 6.3 for patients with a disease duration <2 years, 14.3 for patients with a disease duration of 2–10 years, and 19.0 for patients with a disease duration >10 years.[11] The finding of low LI in the first 2 years is important because it demonstrates

the window of opportunity just after diagnosis, within which intensive treatment might stop disease progression. The new goal for IBD is to block disease progression and damage. Moreover, a post hoc analysis of the CHARM study[13] suggested anti-tumour necrosis factor (TNF) treatments are more efficient early in the IBD course, with results showing differences between placebo and adalimumab for clinical remission rates (at Week 56, results were 19% versus 43% for <2 years; p=0.024; 13% versus 30% for 2–<5 years; p=0.028; and 8% versus 28% for >5 years; p<0.001).

A recent South Korean retrospective analysis classified 670 CD patients into those starting anti-TNF or immune modulators within 2 years of diagnosis and those starting later. The study found that for the early therapy group, times to intestinal surgery (p<0.001), stricturing complications (p=0.002), penetrating complications (p<0.001), and behavioural progression (p<0.001) were significantly longer.[14] A French prospective evaluation of 130 CD patients presented at the 25th United European Gastroenterology (UEG) Week showed that damage increased with disease duration (p<0.001) and, furthermore, the LI was 3.7 for patients who received early anti-TNF therapy (<2 years) versus 12.3 for late anti-TNF therapy (p=0.015).[15] Such data strongly suggest that early introduction of anti-TNF could prevent damage progression and change the natural history of CD.

The CURE study[16] is currently underway and is evaluating the impact of early use of adalimumab on sustained deep remission and long-term outcomes. The aim is to assess if early initiation decreases bowel damage, disability, and surgery over 5 years and whether early use might allow physicians to decrease or even stop treatment to avoid long-term adverse events and reduce healthcare costs. While there is a need for early intensive treatment in some IBD patients, the strategy should not necessarily be applied for all. At an early stage in both CD and UC, indolent disease must be distinguished from aggressive disease. Those with aggressive disease might benefit from a top-down approach, assuring early intensive therapy, while those with indolent disease might benefit from a step-up method, with the possibility of avoiding intensive therapy, immunosuppression, and adverse events.

According to the Paris definition, early CD can be defined as disease duration ≤18 months after diagnosis in patients who have received no previous or current use of immunomodulators and/or biologics with previous or current use of 5-aminosalicylate and/or corticosteroids permitted.[17] If this definition alone is used, there is a high risk of overtreatment, highlighting the need to perform prospective cohort studies identifying early predictors of aggressive IBD. A study of newly diagnosed paediatric CD patients showed upregulation of ileal genes controlling extracellular matrix production at diagnosis was associated with stricturing (hazard ratio [HR]: 1.70; 95% confidence interval [CI]: 1.12–2.57; p=0.0120).[18] Furthermore, data from a sub-cohort for whom ileal gene expression data were available found that biological markers (i.e., anti-*Saccharomyces cerevisiae* antibody [ASCA] immunoglobin A and anti-flagellin [CBir1]-positive) were associated with stricturing and penetrating behaviour.[18]

While awaiting the results of disease modifying trials, we need to adopt new therapeutic strategies, including a T2T approach in IBD, where targets are defined (whether a clinical, biomarker, or composite target) and if not achieved, treatment is intensified or switched.[5,8] For CD, T2T recommendations are composite endpoints consisting of clinical or patient-related outcome remission (defined as resolution of abdominal pain and normalisation of bowel habits), assessed at a minimum of 3 months during active disease, and endoscopic remission (defined as resolution of ulceration), assessed within 6–9 months after the start of therapy.[19] For UC, the T2T target is clinical or patient-related outcome remission (defined as resolution of rectal bleeding and normalisation of bowel habit), assessed at a minimum of 3 months during active disease, and endoscopic remission (defined as resolution of friability and ulceration at flexible sigmoidoscopy or colonoscopy), which should be assessed within 3–6 months after the start of therapy.[19]

The ongoing REACT2 study[20] in CD compares an enhanced T2T treatment with conventional step care to determine whether T2T can reduce CD-related complications, including hospitalisations, at 1 year. Importantly, the T2T strategy is a personalised approach, with desired outcomes in early disease being complete absence of symptoms, no disease progression, no complications or disability, and normal quality of life; the desired outcome in late-disease is stabilisation of non-inflammatory symptoms, no progression or damage or disability, and improved quality of life.[18,21,22]

News Update: CALM Study Results

Professor Jean-Frédéric Colombel

In CD it is unknown whether TC, in which treatment decisions are based on close monitoring of inflammatory biomarkers, results in improved patient outcomes. CALM[23] was a prospective, open-label, multicentre, active-controlled Phase III study evaluating two treatment algorithms in CD, CM, and TC. Patients were randomised 1:1 to CM (where escalation was driven by the CDAI and prednisone use; n=122) or TC (escalation was driven by monitoring of CDAI, faecal calprotectin [FC], CRP, and prednisolone use; n=122).

For the TC arm, even if patients were doing well, treatment was escalated if one of the biomarkers was raised. Treatment in both arms was escalated in a stepwise manner from no treatment to adalimumab induction, followed by adalimumab every other week, adalimumab every week, and lastly to both weekly adalimumab and daily azathioprine. During the post-randomisation treatment period, treatment was escalated at 12, 24, and 36 weeks if patients met any of the post-randomisation treatment failure criteria.

For the CM arm, CALM failure was considered to occur at Week 1 if CDAI decreased by <70 points compared with baseline or CDAI was >200. For the TC arm, treatment failure was considered to occur at Week 1 for CDAI ≥150, CRP ≥5 mg/L, FC ≥250 µg/L, and prednisone use at Week 0. For Weeks 11, 23, and 35, CALM failure criteria for CM were a CDAI decrease <100 points compared with baseline or CDAI ≥200 and prednisone use a week prior to the visit, while for TC failure, the criteria were CDAI ≥150, CRP ≥5 mg/L, FC ≥250 µg/L, and prednisone use a week prior to the visit.[23]

Inclusion criteria included adults aged 18–75 years with ileal, colonic (including rectal), or ileocolonic CD with moderate-to-severe CD with or without systemic corticosteroids. Exclusion criteria included previous or current use of biologics or immunomodulators, more than two previous courses of corticosteroids, or current use of corticosteroids for >3 months before screening.[23] The primary endpoint was mucosal healing (CDEIS <4) and no deep ulcerations (assessed 48 weeks after randomisation). Secondary endpoints included deep remission, biologic remission, mucosal healing, complete endoscopic response, and steroid-free remission, among others.

For CALM, of 460 patients screened, 244 met the inclusion criteria and were randomised to CM (n=122) or TC (n=122). The study was completed by 93 CM patients (76.2%) and 90 TC patients (73.8%), with reasons for discontinuation including adverse events, withdrawal of consent, loss to follow-up, and lack of efficacy. Baseline characteristics showed mean disease duration was 0.86 years in the CM group and 1.04 years in the TC group, making CALM subjects one of the earliest populations ever studied in anti-TNF clinical trials.

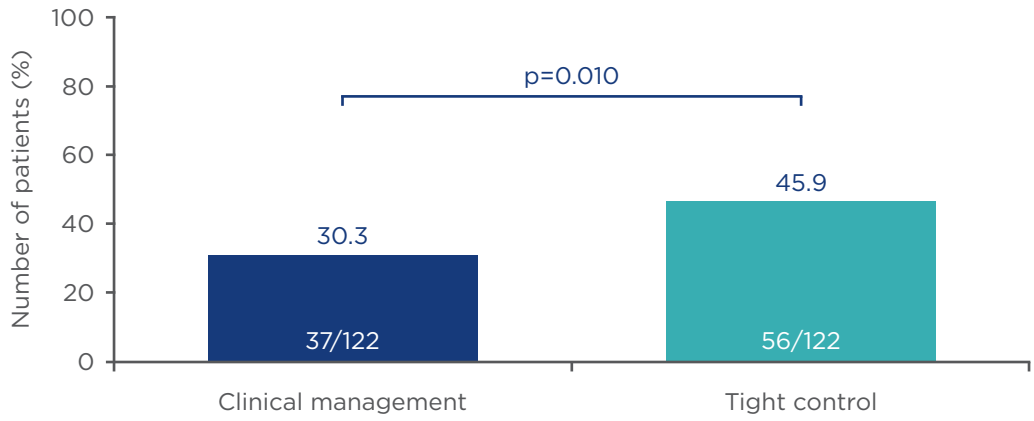

Figure 1: CALM primary endpoints at 48 weeks after randomisation (mucosal healing [CDEIS <4] and no deep ulcerations). Higher rates of mucosal healing and no deep ulceration were observed in early Crohn's disease when treating to a target of biomarker levels (C-reactive protein and faecal calprotectin), compared with symptom-driven clinical management.

CDEIS: Crohn's disease endoscopic index of severity.

Adapted from Colombel et al.[24]

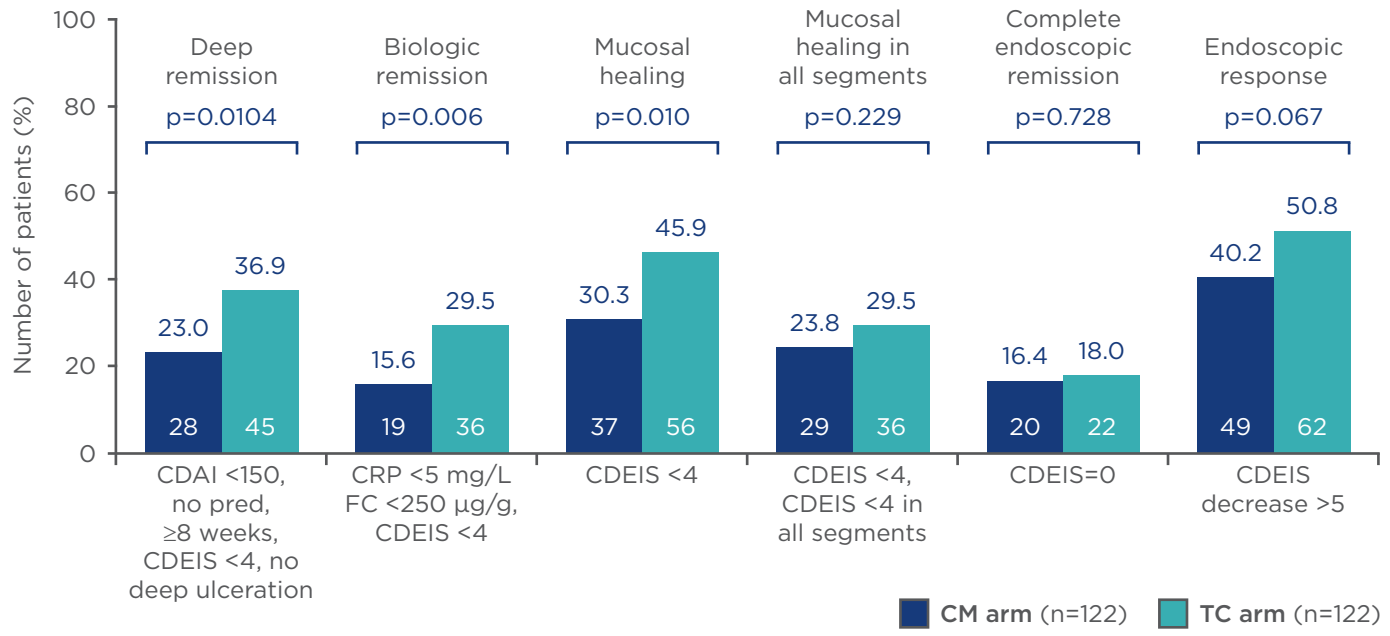

Figure 2: CALM secondary endpoints at 48 weeks after randomisation. Higher rates of mucosal healing and deep remission were observed in early Crohn's disease when treating to a target of biomarker levels (C-reactive protein and faecal calprotectin), compared with symptom-driven clinical management.
CDAI: Crohn's disease activity index; CDEIS: Crohn's disease endoscopic index of severity; CM: clinical management; CRP: C-reactive protein; FC: faecal calprotectin; pred: prednisone; TC: tight control.
Adapted from Colombel et al.[24]

CALM results showed that the primary endpoint of mucosal healing (CDEIS <4) and no deep ulceration was achieved in 45.9% in the TC arm versus 30.3% in the CM arm (p=0.010) (Figure 1).

The TC arm was also strongly positive for a number of secondary endpoints at Week 48, including deep remission (p=0.0104), biologic remission (p=0.006), mucosal healing (p=0.010), and endoscopic response (p=0.067). However, CALM results were not significant for mucosal healing in all segments (p=0.229) and complete endoscopic remission (p=0.728) (Figure 2). Furthermore, at all time points, significantly more patients achieved steroid-free remission in the TC than CM arm (p=0.009 at 11 weeks, p=0.003 at 23 weeks, p=0.007 at 35 weeks, and p<0.001 at 48 weeks).

An analysis exploring different treatment regimens at Weeks 0, 1, 24, and 36 showed treatment was escalated and tapered earlier in the TC arm compared with the CM arm. Since more patients in the TC group escalated to adalimumab every week at 12 weeks and to adalimumab every week plus azathioprine at 24 weeks than in the CM group, investigators predicted side effects would be higher in the TC group. This, however, was not the case. Serious adverse events occurred in 20.5% of the CM group versus 18% of the TC group and most notably serious infections occurred in 9.8% of the CM group versus 4.9% of the TC group.

To conclude, CALM represents the first study demonstrating that the TC approach, using objective data (inflammation biomarkers), improves outcomes in CD compared with symptom-driven care. Results give rise to the view that managing CD patients by clinical symptoms alone may not adequately control underlying inflammation and that biomarker levels can guide treatment escalations, leading to superior endoscopic and clinical outcomes. Finally, the TC approach did not lead to increased safety signals.

Treating to Target in Inflammatory Bowel Disease: At What Cost?

Professor Geert D'Haens

Several patients had escalated treatment to weekly dosing in CALM, raising the question of whether such expenditure is cost-effective. Financial costs represent only one aspect of IBD, with the need to also take quality of life, physical wellbeing, and psychological impact into

consideration. In IBD, benefits from optimal use of therapies through T2T include obtaining sustained deep remission, reductions in accumulation of intestinal damage, complications and disability, reduced need for surgery, relief of extraintestinal manifestations, therapy withdrawal, improved quality of life, and improved work and social function. In children and adolescents, an additional goal is restoring growth, and for all patients, the ultimate goal is a return to normal life.

The CALM study demonstrated that symptomatic and endoscopic remission was reached more frequently using TC than CM. Furthermore, the study showed TC resulted in earlier and increased use of adalimumab. More intensive immunosuppression with adalimumab, however, did not result in increased safety signals during the year of the trial. Looking at serious infections, anal abscesses occurred in four patients of the CM group (3.3%) versus zero of the TC group, and most other infections occurred equally frequently between the groups.

CALM showed:

- Significantly fewer CD-related hospitalisations occurred in the TC group (13.2 events per 100 patient years) than the CM group (28.0 events per 100 patient years) (p=0.021).[23]
- When pooling adverse outcomes, at 48 weeks fewer hospitalisations or complications were observed in the TC group (14.8%) than the CM group (20.5%), although the difference was not statistically significant (p=0.240).[23]
- The rates of CD-related surgical procedures after randomisation were 6.6 events per 100 patient years for the TC arm versus 8.7 events per 100 patient years in the CM arm (p=0.582).[23]
- The TC and CM time to CD-related hospitalisation or serious complications began to separate at Week 15 after remission, favouring TC, but the difference was not statistically significant (HR: 0.7; 95% CI: 0.4–1.3; p=0.249).[23]

However, there was an early significant separation in the time to CD flare between the CM and TC groups (HR: 0.4; 95% CI: 0.2–0.8; p=0.012), with flare defined as an increase in CDAI score by ≥70 points from 1 week prior to randomisation and a total CDAI score of >220.[23]

The 1-year follow-up used in CALM was shorter than the REACT trial,[25] in which patients were assigned to early combined immunosuppression with a TNF antagonist and antimetabolite or conventional management, and followed for 2 years. Patients were reviewed every 3 months and if they were not in clinical remission, treatment was escalated. No difference in any adverse outcomes was seen at 12 months, but results at 24 months favoured rapid treatment escalation based on symptoms. For the REACT2 study, which is anticipated to be reported in 2018, treatment escalation is based on endoscopy.[20]

For the CALM economic analysis, patients were categorised by disease state according to CDAI, with remission (defined as CDAI <150), moderate disease (CDAI ≥150 to <300), severe disease (CDAI ≥300 to <450), and very severe (CDAI ≥450). The model used a previously published health state structure,[26] and leveraged an analysis relating CDAI to the EuroQOL five dimensions questionnaire (EQ-5D) on health-related quality of life,[27] and a study relating CDAI to resource utilisation[28] to estimate QALY and other direct medical costs. CD-related hospitalisations and adalimumab injections were based on data from the CALM trial.

At the simplest level, when people do not feel well, they visit the doctor, with hospitalisation representing one of the main drivers of healthcare utilisation and expense. Calculations for the incremental cost-effectiveness ratio (ICER) take into account effects and costs of interventions but also improvements in quality of life. Gains in QALY can be calculated from CDAI distribution (from the CALM study) multiplied by EuroQOL five dimensions questionnaire (EQ-5D) scores according to CDAI.[27]

Direct medical costs are the sum of hospitalisation costs, adalimumab costs, and other direct medical costs. The ICER is calculated based on the difference between the TC and CM arms by dividing the direct medical costs by QALY. Results showed predicted time in remission was 62.1% for the TC arm versus 47.3% for the CM arm (difference: 14.8%); the CD-related hospitalisations were 0.13 for the TC arm versus 0.28 per person year for the CM arm (difference: -0.15); the number of adalimumab doses (40 mg) were 30.87 for the TC arm versus 24.72 for the CM arm (difference: 6.15); and other direct medical costs were £1,298 for the TC arm versus £1,524 for the CM arm (difference: -£226), CD-related hospitalisation costs were £1,128 for the TC arm versus £2,398 for the CM arm (difference: -£1,270), and adalimumab costs were £10,870 for TC arm versus £8,705 for the CM arm (difference: £2,165).[3]

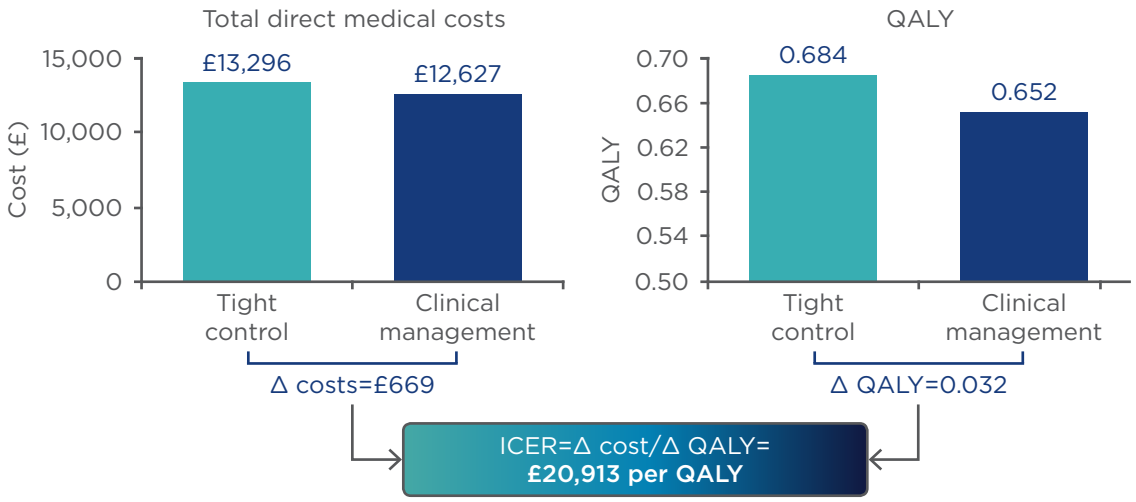

Figure 3: Economic analysis from the CALM study.
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years.
Adapted from Panaccione et al.[29]

Over the 48 weeks, the total direct medical costs were £13,296 for the TC arm versus £12,627 for the CM arm, giving a difference of £669. QALY were 0.684 for the TC arm versus 0.652 for the CM arm, giving a QALY difference of 0.032. The difference in costs of £669 divided by the difference in QALY of 0.032 produced an ICER of £20,913 per QALY (Figure 3). According to UK NICE guidelines, interventions costing less than £30,000 per QALY gained can be considered cost-effective.[30] In conclusion, in the CALM study TC in CD led to improved clinical outcomes, reduced CD-related hospitalisation, and improved patient quality of life. Furthermore, based on CALM data, a TC strategy appears cost-effective compared with CM.

Discussion

Considering how the CALM study could be translated into clinical practice, Prof Colombel said that the most important message was the need to regularly monitor symptoms and biomarkers.

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OUTCOME OF PERORAL ENDOSCOPIC MYOTOMY IN TREATMENT-NAÏVE VERSUS PRIOR TREATMENT FAILURE CASES OF ACHALASIA

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Achalasia cardia (AC) is a neurodegenerative disease characterised by the absence of normal peristalsis and relaxation of the lower oesophageal sphincter (LOS). The motility of the oesophageal body cannot be restored using the currently available treatment options, like pneumatic balloon dilatation, Heller myotomy, botulinum toxin injections, and peroral endoscopic myotomy (POEM). Therefore, we offer the optimum palliative care to these patients, mainly by disrupting the LOS. POEM has emerged as an efficient endoscopic treatment option for AC, and multiple studies with short-to-medium-term follow-up have confirmed the utility of POEM in these patients. However, most of these studies have evaluated the efficacy of POEM in treatment-naïve cases of AC, whereas there are limited data from studies that assessed the outcome of POEM in prior treatment failure cases. Previous treatment has been shown to induce submucosal inflammation and fibrosis, and can therefore influence the technical and clinical outcomes of subsequent treatment. With this aim, we evaluated and compared the outcome of POEM in treatment-naïve and prior treatment failure cases of AC in approximately 500 patients using a retrospective analysis of a prospectively maintained database.

The baseline characteristics were similar in both patient groups, except for the age and proportion of patients with sigmoid achalasia. The prior treated achalasia group consisted of older participants and included more patients with sigmoid achalasia than the treatment-naïve group. Besides these characteristics, the other baseline characteristics, such as the type of achalasia and basal LOS pressure, were similar in both groups. In addition, pneumatic balloon dilatation was the most common treatment type in the prior treated group (84%), followed by Heller myotomy (10%). POEM could be successfully completed in the majority of patients in both the groups; however, severe submucosal fibrosis was the most common reason for premature termination of POEM procedure, although it was found in only 1.8% of patients. Severe submucosal fibrosis was encountered in equal numbers of patients in both the groups, and therefore prior treatment may not be the only factor leading to submucosal fibrosis, and other factors like long disease duration and mucosal oedema may also play an important role. The occurrence of major and minor adverse events was similar in both groups, which implies that POEM can be safely accomplished in previously treated patients. The procedure duration was longer in the prior treatment group, but this was not significant when taking other factors into account, such as dilatation of the oesophagus (>6 cm), type of knife used (with or without water jet), occurrence of an adverse event, type of AC, and disease duration. The clinical success was identical in both of the groups at short-term (6 months: ~90%) and long-term (3 years: ~80%) follow-up.

We also evaluated and compared gastro-oesophageal reflux disease (GORD) between these groups with symptom analysis, oesophagogastroduodenoscopy, and 24-hour pH analysis. GORD was detected in approximately a quarter of patients in the treatment-naïve group and one-third of patients in the prior treatment failure group. There was a poor correlation between symptoms, erosive oesophagitis, and 24-hour pH results; only half of the patients with positive 24-hour pH results had symptoms suggestive of GORD, meaning that symptoms alone may not be a reliable indicator of

GORD and objective documentation of GORD by pH study is required to guide therapeutic decisions.

To conclude, POEM is equally effective for treatment-naïve and prior treatment failure patients with achalasia and has the potential to be the first-line treatment modality in prior treatment failure patients with achalasia. Randomised trials are required to compare the effectiveness of POEM with other established treatment options, such as pneumatic dilatation and Heller myotomy.

NUTRITIONAL SUPPORT IN GASTROPARESIS: PERCUTANEOUS ENDOSCOPIC GASTROSTOMY WITH JEJUNAL EXTENSION: THE ULTIMATE SOLUTION? A RETROSPECTIVE ANALYSIS

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Keywords: Endoscopy, enteral nutrition, gastroparesis, percutaneous endoscopic gastrostomy.

Gastroparesis is characterised by delayed gastric emptying in the absence of mechanical obstruction.[1] In our tertiary referral centre, patients are treated with a stepwise approach, starting with dietary and lifestyle advice, and prokinetics. When these initial measures fail, in the presence of malnutrition, patients are offered 3 months of nasoduodenal tube feeding with 'gastric rest' and eventually placement of a percutaneous endoscopic gastrostomy with jejunal extension (PEG-J). In our study, presented at UEG Week 2017, we aimed to evaluate the effect of nutritional treatment entities in patients with gastroparesis on weight gain and symptoms.

Retrospectively collected data of all referred gastroparesis patients between 2008 and 2016 were reviewed. A total of 86 gastroparesis patients, 71% of which were female, between the age of 20 and 87 years (mean age: 55.81 years) were analysed. Aetiologies were idiopathic (37.2%), diabetes (26.7%), post-surgical (26.7%), and other (9.4%). Of the 86 patients, 50 had adequate responses to dietary advice and prokinetics, while the other 36 were treated with 3 months of gastric rest. The mean weight gain in symptom responders was 3.6% (2.5 kg; p=0.018) and 3.3% (2.1 kg; p=0.027) in non-responders.

After 3 months of gastric rest, the 19 non-responders continued treatment with enteral feeding through PEG-J. A significant weight gain was seen in symptom responders (n=14, 74%) to PEG-J (8.3%, 5.04 kg; p=0.016) within 6 months after PEG-J placement. Four patients did not show symptom response to PEG-J treatment; however, the patients did gain weight (mean weight gain: 6 kg, 8.1%; p=0.089). The outcome for 1 patient was missing. On long-term follow-up, only 3 patients (16.7%) were able to resume complete oral intake and the PEG-J was removed after 11 months. In 83.3% of patients, the PEG-J was still in use, with a mean treatment time of 962 days. The most frequent complication associated with the treatment was luxation of the jejunal extension to the stomach, which occurred in 32% of patients.

Regarding enteral feeding in gastroparesis, guidelines indicate a trial with enteral feeding before placement of a long-term device to see

whether or not enteral feeding is tolerated.[2] Some patients may find the 3-month period of nasoduodenal feeding long, but the length of such intervention remains the topic of further investigation. Historically, surgical jejunostomies have often been used for long-term nutritional support in gastroparesis, but this technique is associated with a lower placement success rate of 68%,[3,4] and a relatively high complication rate of 10%,[5] hence our preference for the endoscopic placement approach.

An interesting phenomenon we observed was that, in general, all types of nutritional support measures led to an increase in weight but not always to a decrease in symptom severity. We have not been able to discriminate a group that is unlikely to show a symptom response to enteral feeding, either with demographic or scintigraphic parameters. The retrospective nature of the study did not allow assessment of other factors, including psychological influences, but we postulate that visceral hypersensitivity plays a paramount role in patients who do not show symptom response. We therefore believe that systematic assessment of mood and anxiety disorders should be an integral element of the diagnostic work-up and therapeutic plan in patients with gastroparesis.

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FIVE-YEAR ITALIAN REGISTRY OF DIVERTICULOSIS AND DIVERTICULAR DISEASE (REMAD): A LOW PROGRESSION RATE OF DISEASE DURING THE FIRST YEAR OF FOLLOW-UP

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Keywords: Colonic diverticulosis, diverticulitis, recurrence, registry, symptomatic uncomplicated diverticular disease (SUDD).

INTRODUCTION AND AIMS

Traditionally, the lifetime risk of developing diverticulitis, the most common clinical complication in diverticular disease, is cited as 10–25%; this high rate of progression, however, has been contradicted by a recent colonoscopy-based retrospective study reporting that only approximately 4% of patients with diverticulosis develop acute diverticulitis.[1] At present, a small number of studies, mainly retrospective, have evaluated the natural history of diverticulosis and diverticular disease.[1-3]

The aim of this study was to assess the incidence of new cases of symptomatic uncomplicated diverticular disease (SUDD) and diverticulitis, and recurrence of diverticulitis after 1-year of follow-up, in a cohort of patients with colonic diverticula.

METHODS

The Italian Study Group on Diverticular Disease (GRIMAD) scientific association promoted the creation of the Registry of Diverticular Disease (REMAD),[4] an ongoing 5-year prospective, observational, multicentre, cohort study, involving 47 centres, both academic and non-academic. Each centre was required to recruit at least 20 consecutive patients over 2 months. A total of 1,255 consecutive patients with colonic diverticula were initially considered, but five centres recruited <20 patients, and, therefore, those centres and corresponding recruited patients were excluded from the study (n=38). The median rate of non-adherence of patients to the registry was 22% (range: 5.0–36.4%). Inclusion criteria were informed consent, age ≥18 years, and endoscopic or radiological-confirmed colonic diverticula. Outpatient visits or telephone appointments were scheduled every 6 months.

At entry, patients were categorised into three subgroups according to the following criteria:

- Diverticulosis: presence of colonic diverticula in the absence of abdominal symptoms.
- SUDD: recurrent abdominal symptoms as abdominal pain and/or changes in bowel habit, attributed to diverticula in the absence of overt inflammation.[5-7]
- Previous diverticulitis (PD): patients who have experienced at least one episode of acute diverticulitis in the past.

The number of new cases of SUDD, diverticulitis, and recurrence of diverticulitis after 1 year of follow-up was evaluated. Patients were allowed to continue their therapy, if any. Logistic regression (adjusted for age <60 years, sex, BMI ≥25 kg/m^2, Charlson Comorbidity Index ≥3, gastrointestinal comorbidities, family history for diverticular disease, use of non-steroidal anti-inflammatory drugs, antiplatelet, anticoagulants, proton pumps inhibitors, and statins) was performed to identify patient features associated with new occurrence of SUDD and diverticulitis.

RESULTS

A total of 1,217 patients (556 [45.7%] female, mean age: 66.1±9.9 years, BMI: 26.1±3.9 kg/m^2) with a baseline diagnosis of diverticulosis (57.9%), SUDD (24.7%), and PD (17.4%) were included in the study. At 12 months, 922 patients (53.1%, 29.8%, and 17.1% with diverticulosis, SUDD, and PD, respectively) were followed; 11.9% of patients were lost at follow-up and data of 15.5% were not up to date.

During follow-up, 33 (6.3%) baseline diverticulosis patients developed SUDD and 4 (0.7%) developed diverticulitis (1 perforation), 4 (1.6%) baseline SUDD patients developed diverticulitis (no complications), and 14 (9.4%) patients who entered with PD developed a recurrence of diverticulitis (including 3 patients with complications such as perforation, abscess, and stenosis). The median time from the first episode of diverticulitis to recurrence was 4.5 years (0.003–15.04); no patients required surgery. The main characteristics of patients who developed diverticulitis are reported in Table 1. Logistic regression showed that the female sex was associated with subjects who changed subgroup from diverticulosis to SUDD (odds ratio: 2.26; 95% confidence interval: 0.97-5.22; p=0.05, barely missed). No features associated with recurrence of diverticulitis could be identified.

Table 1: Main characteristics of patients who developed diverticulitis.

	Female	Age (mean years)	BMI ≥25 kg/m^2
Diverticulosis (n=4)	3 (75%)	59.7±5.7	2 (50%)
Symptomatic uncomplicated diverticular disease (n=4)	2 (50%)	63.2±18.3	3 (75%)
Previous diverticulitis (n=14)	12 (85.7%)	64.7±11.5	7 (50%)

CONCLUSION

These preliminary data show that, during an observation period of 1 year, progression from diverticulosis to SUDD occurred in <10% patients, and was associated with female sex. The overall incidence of diverticulitis was very low (2.3%), whereas recurrent diverticulitis was not uncommon. This observational study showed that, although the vast majority of patients did not show progression of disease, diverticulitis recurrence represents an important clinical challenge.

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NEW INSIGHTS IN LIVER AND PANCREATIC STELLATE CELLS: THE ROLES OF TOLL-LIKE RECEPTOR 5

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Keywords: Intercellular communication, microbiota, organ fibrogenesis, stellate cells, toll-like receptor (TLR).

Hepatic stellate cells are responsible for liver tissue's ability to store vitamin A and 80% of whole-body retinol as cytosolic lipid droplets of retinyl palmitate.[1] They are distributed in the space between the parenchymal and sinusoidal cells.[2] Hepatic stellate cells are physiologically quiescent and are characterised by epithelial morphology.

Liver insult, damage, and/or epigenetic modifications cause the transdifferentiation of stellate cells into myofibroblasts.[3] Once the stellate cells transactivate into mesenchymal cells, they can infiltrate the liver parenchyma and are responsible for the collagen secretion, which can lead to liver fibrosis, cirrhosis, and tumourigenesis.[3,4]

Pancreatic stellate cells (PSC) constitute the pancreas stroma. The cells carry out various functions, including the formation of the extracellular matrix, stimulation of amylase secretion, phagocytosis, and contributing to immunity.[5] Quiescent PSC are characterised by vitamin A droplets; once active, they assume a myofibroblast-like morphology and are responsible for the fibrogenesis observed in pancreatitis and pancreatic ductal adenocarcinoma.[6] Furthermore, it has been shown that PSC support tumour metabolism by inducing autophagic alanine secretion.[7] Until now, the role exerted by PSC has been unclear, and it is not known if they exert a tumour-suppressing or a tumour-sustaining effect.

Our study highlights a possible intercommunication existing between the stellate cells, other pancreatic and liver cells, and the microbiota. *In vitro* studies show that LX2[8] and HPSC 2.2[9] immortalised stellate cells can be easily treated with low levels of tumour growth factor beta (TGF-β1), leading to their transdifferentiation into myofibroblasts. TGF-β1 was able to stimulate the stellate cells, promote their activation, and their change from a quiescent state to an active one, which characterises these cells in their liver and pancreatic tissue environment. The responsiveness to TGF-β1 highlights the fact that the stellate cells can be activated by signalling coming from both neighbouring and more distant cells. In particular, the presence of tumour cells in the surrounding parenchyma could be also responsible for stellate cell activation through the secretion of several growth stimulating factors, including TGF-β1.[10]

Currently, apart from their simple vitamin and fat storing role, the function of stellate cells is not yet fully understood; they could play a strategic role during tumourigenesis and promote intra and intercellular signalling, actively participating in the tumour environment.

Interestingly, TGF-β1 signalling was responsible in the proposed model for inducing the expression of toll-like receptor (TLR)5. This member of the TLR family is known for being easily activated by the bacterial protein flagellin. It was observed that knocking down the mRNA and protein level of TLR5 completely disabled TGF-β1 efficacy, leaving the liver and PSC in a quiescent state. The expression of TLR5 was essential for the stellate cells to acquire their active status and the efficacy of TGF-β1 was dispensable in cells knocked down for TLR5.

The importance of TLR5 in stellate cell activation offers new perspectives for understanding the mechanisms underlying stellate cells' involvement in the tissue environment: in particular, the sensitivity of stellate cells to stimuli coming from micro-organisms populating the host body and the ability of micro-organisms to activate molecular and morphological changes in cells that play a specific role in the structure and functioning of the tissue or organ. Understanding the mechanisms of organ fibrogenesis in correlation with tumourigenesis and the influence of microbiota will open new directions for future treatment of diseases affecting the upper-midgut area of the human body.

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ASSESSMENT OF EXHALED BREATH CONDENSATE FOR NON-INVASIVE DIAGNOSIS OF GASTRO-OESOPHAGEAL REFLUX DISEASE IN CORRELATION WITH MII-PH AND PEPTEST

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Keywords: Capillary electrophoresis, exhaled breath condensate (EBC), gastro-oesophageal reflux disease (GORD), ionic profile, multichannel intraluminal impedance and pH monitoring (MII-pH), non-invasive sampling, pH.

Gastro-oesophageal reflux disease (GORD) is widely defined as a condition that develops when the refluxed material of the stomach content causes troublesome symptomatology and/or complications.[1] The 24-hour multichannel intraluminal impedance and pH monitoring (MII-pH) is presently the gold standard diagnosis tool, but it is invasive and expensive. There is, however, no suitable, non-invasive substitute diagnostic method applicable for GORD diagnosis in clinical practice.

Exhaled breath condensate (EBC)[2] and saliva[3] are two easily obtained, non-invasive samples that bear promise in monitoring patients suffering from GORD. The aim of this study was to investigate the prospects of these samples in non-invasive diagnostic approaches to GORD. We compared the pH and total ionic profile of EBC, analysed by capillary electrophoresis with contactless conductometric detection, MII-pH, and salivary Peptest in a group of patients with acid reflux (pH<4), weakly acid reflux (pH 4–7), and healthy controls. Patient classification into the three groups was based on the results obtained from MII-pH.

A specially designed EBC sampler[4] was used to collect the EBC samples from 2–5 exhalations. The EBC sample was split into two aliquots, typically about 10 µL each. In one aliquot the pH was measured with a pH-microelectrode. Total ionic concentration profile, encompassing anions, cations, and organic acids, was analysed by capillary electrophoresis in the second aliquot. Concurrently, saliva samples were acquired from the patient and healthy groups, and analysed by the Peptest lateral flow device. From all ions present in EBC and pH measurements, a few significant markers were identified. First, the pH was significantly elevated in the group with acid reflux (mean pH: 7.13; interquartile range [IQR]: 6.83–7.47; $p<0.01$) and in the group with weakly acid reflux (mean pH: 7.37; IQR: 7.18–7.57; $p<0.01$) compared to healthy controls (mean pH: 6.8; IQR: 6.65–6.99). Among the ions analysed by capillary electrophoresis, concentration of butyrate (BA) was the most significant parameter. BA was significantly elevated ($p<0.01$) in both the acid reflux and weakly acid reflux patient groups compared to healthy subjects; mean BA was measured at 2.29 µM, 3.33 µM, and 0.69 µM, respectively. Other ions from the EBC samples were also elevated, but the statistical significance was lower.

Pepsin was analysed in all samples with the Peptest, but its incidence could not distinguish between the

groups of healthy and weakly acidic reflux patients. In the groups of patients with acid reflux, the incidence of high pepsin concentration (>75 ng/mL) was found only in 50% of the patients. We found that pH and BA concentration in EBC were the most statistically significant markers. Both can be measured easily and quickly, in <5 minutes; therefore, the initial screening for these markers can provide a fast and non-invasive check to pre-select the patients with possible GORD positivity. Unfortunately, the markers are not sensitive enough to distinguish the weakly acid and acid reflux, but can potentially be used to reduce the diagnostic cost and avoid unnecessary invasive MII-pH testing. Unlike the EBC, pepsin analysis in saliva did not provide any diagnostic value.

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PERFORMANCE OF A DIAGNOSTIC ALGORITHM FOR FUNCTIONAL GASTROINTESTINAL DISORDERS

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Keywords: Diagnosis, functional dyspepsia, functional gastrointestinal disorders, irritable bowel syndrome, management, primary care.

Functional gastrointestinal disorders (FGID), such as irritable bowel syndrome and functional dyspepsia, are poorly managed in many healthcare settings. Delays in diagnosis and the unnecessary use of invasive investigations are common. Although symptom-based diagnostic criteria and effective evidence-based treatments are available, most clinicians outside FGID specialist centres do not use these criteria in practice and are not confident in diagnosing without specialist input. In fact, gastroenterology referrals for suspected FGID can represent up to half of ambulatory

gastroenterology consultations and often exceed the capacity of publicly funded tertiary referral centres. This results in not only extremely long waiting lists but also poor patient outcomes and high use of healthcare resources due to delayed diagnosis and the lack of effective management.

The aim of this study was to determine whether an alternative model of care could be used to facilitate a safe and timely diagnosis and provide effective management without direct specialist input. Participants from the routine waiting list of a tertiary referral centre were randomised to a waiting list control group or algorithm group (1:2). A total of 315 patients were invited, with 109 completing intake (control n=20, algorithm n=89). Participants in the algorithm group were screened with a questionnaire and routine tests (without consultation). Almost two in five patients (39%) had clinical signs requiring a gastroenterologist review, which resulted in prompt detection of organic disease in almost a third. Organic diseases diagnosed during the study included inflammatory bowel disease, neoplasm, pancreatic insufficiency, reflux oesophagitis, and iron deficiency, the cause of which was unknown. Half of those screened had no clinical warning signs and received a letter clearly stating and explaining the FGID diagnosis. Information about FGID and evidence-based management options, such as the low FODMAP diet (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols), and psychological therapies, as well as resources and how to access these services, was also provided to both the patient and referring doctor.

All but one participant read the diagnostic letter, and those who read it found it to be useful because it provided a diagnosis, reassurance, and management options. Interestingly, only a quarter of patients discussed the letter with their physician, yet most (80%) engaged in some form of management regime by 6 weeks post-diagnosis. Dietary management options were used almost twice as often as psychological therapies, and do-it-yourself options were preferred. Symptomatic improvement was reported in 61% of respondents at 6 weeks, and 86% at 1 year post-diagnosis. The approach was at least moderately acceptable to 68% of participants and 100% of referring doctors. The preference for self-management options identifies an important opportunity to safely address a clear clinical need. Similarly, the poorer uptake of psychological therapies, such as gut-directed hypnotherapy, which have been shown to be very effective in reducing global symptom burden, highlights the need for better communication regarding the brain-gut axis and the ability to harness this to achieve symptomatic improvement.

This study has shown that a simple screening algorithm can be used to improve the detection of organic disease and provide timely, accurate diagnosis of and evidence-based management options for FGID without gastroenterologist consultation. This pathway has been shown to be safe and, importantly, safer than current triaging of referrals. The process was feasible to implement and acceptable to both patients and doctors. These pilot data are encouraging and justify a further larger scale evaluation within primary care.

EPIDEMIOLOGY OF ALCOHOLIC LIVER DISEASE AND NON-ALCOHOLIC FATTY LIVER DISEASE. HOW TO DIFFERENTIATE BETWEEN THEM AND THEIR IMPLICATIONS FOR CARDIOVASCULAR RISK

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Keywords: Alcoholic liver disease (ALD), cardiovascular risk, genetic factors, non-alcoholic fatty liver disease (NAFLD).

Fatty liver disease encompasses a spectrum of diseases, including alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD), one type of which is non-alcoholic steatohepatitis (NASH). However, it is increasingly recognised that a large number of patients have both harmful alcohol consumption and metabolic risk factors, such as obesity, diabetes, and dyslipidaemia.

Independent of which aetiology predominates, there is a possibility of disease progression to advanced liver disease, cirrhosis, or hepatocellular carcinoma (HCC). The only distinction between ALD and NAFLD is daily alcohol consumption of <30 g for men and <20 g for women. Alcohol consumption above these limits represents ALD.[1] Harmful alcohol consumption is a major burden to an individual's health in general, and particularly for the liver. According to the World Health Organization (WHO) noncommunicable diseases 2014 report,[2] an estimated 3.3 million deaths, or 5.9% of total deaths worldwide, were attributable to alcohol consumption in 2012. Approximately half a million of these were as a result of liver cirrhosis, which represents 0.9% of total deaths, 10.4% of alcohol-attributable deaths, and 0.6% of all disability adjusted life-years. Data from the European Union (EU) have shown that 41% of liver-related deaths, excluding primary liver cancer, are attributable to alcohol and 46% are of unknown aetiology. However, as recently reviewed by Sheron,[3] it is possible that a large percentage of the undisclosed causes are ALD and that around 60–80% of liver-related deaths in Europe are, in fact, due to excess alcohol consumption.

Although the disease has a slow progression, usually >10 years, patients tend to present with symptoms in the later stages of disease, when they already have complications such as ascites, jaundice, infections, gastro-intestinal bleeding, and HCC. In fact, HCC is one of the more serious consequences of alcoholic liver disease, and it was recently reported that alcohol is the second leading cause of HCC, being responsible for about one-third of all HCC.[4] NAFLD is an umbrella term for several different fatty liver diseases, including steatosis, NASH, and cirrhosis. For many years, there has been a dichotomy between steatosis and NASH; steatosis is characterised by either pure steatosis or steatosis and mild lobular inflammation, whereas NASH is defined by hepatocyte ballooning plus lobular inflammation. Recently, this distinction with regard to diagnosis does not seem so important, since the major prognostic factor in long-term follow-up is the presence and degree of fibrosis.[5,6]

The prevalence of NAFLD worldwide is estimated to be 25.2%, the highest being in the Middle East and the lowest being in Africa, which could be related to the nutritional and physical activity status in these areas.[7] NAFLD incidence is more frequent in males, increases with age, and increases in the presence of a metabolic syndrome, such as hypertension, obesity, or dyslipidemia.[8] However, a certain degree of discrepancy between excessive caloric intake and NAFLD in areas such as Asia and South America suggests that ethnicity and genetic factors also play a significant role in the development of NAFLD. Recently, two variants of the genes *PNPLA3* and *TM6SF2* were found to have a strong effect on the risk and severity of NAFLD and ALD. Additionally, a variant of the *MBOAT7* gene was also associated with ALD; however, its association with NAFLD is still to be proven.[9] NAFLD is linked to an increased risk of cardiovascular disease; several studies have demonstrated that the major cause of death in patients with NAFLD is cardiovascular related, including a recent meta-analysis of 8 studies, as well as a 26-year long-term study that reported 43% of deaths of NAFLD patients was due to cardiovascular disease.[10]

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EDITOR'S PICK

Mandavdhare et al. give an excellent overview of extrapulmonary tuberculosis, with a special focus on abdominal involvement. Unfortunately, this topic requires the attention of all, due to its rising incidence and increasing global migration. There are valuable paragraphs summarising the clinical presentation, diagnostic approach, and relevant comorbidities, as well as challenges in the treatment of the disease and confirmation of its success.

Dr Jan Bornschein

RECENT ADVANCES IN THE DIAGNOSIS AND MANAGEMENT OF ABDOMINAL TUBERCULOSIS

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ABSTRACT

Abdominal tuberculosis and its protean manifestations still create a diagnostic challenge for clinicians and remain an important concern in the developing world. Crohn's disease, which is being increasingly recognised in countries where intestinal tuberculosis is prevalent, needs to be differentiated as the two diseases resemble each other in their clinical presentation, and in their radiological, endoscopic, and histological findings. New diagnostic modalities and scoring systems have facilitated the differentiation of Crohn's disease from intestinal tuberculosis with good accuracy. Randomised trials have shown 6 months of therapy to be equivalent to longer durations of treatment for patients with abdominal tuberculosis. This review focusses on the recent advances in diagnosis and management of abdominal tuberculosis.

Keywords: Abdominal tuberculosis (ATB), acid-fast *bacilli*, colonoscopy, computed tomography (CT), intestinal tuberculosis (ITB), polymerase chain reaction (PCR).

INTRODUCTION

Since its first description thousands of years ago, tuberculosis (TB) has ailed humanity and still haunts the human race. TB continues to be the top killer out of all infectious diseases worldwide, particularly in developing countries, according to the World Health Organization (WHO) global TB report in 2016.[1] Extrapulmonary TB (EPTB) accounts for 15–20% of all cases and involvement of the abdomen is reported in 3.0–6.7% of EPTB cases.[1-3] A recent report from India, which included 2,219 patients with EPTB, found that 11% of patients had infection with abdominal involvement; the abdomen was the third most common site after the lymph nodes and the pleura.[4] Due to the insidious course of the disease, the nonspecific and protean manifestations of abdominal TB (ATB), and the difficulty in establishing the correct diagnosis, a clinician needs to have a high index of suspicion to reach a correct diagnosis.[5] Poor socioeconomic status, undernutrition, poor hygiene, immunosuppression (such as HIV or AIDS), use of steroids or biologicals, history of a solid

organ transplant (particularly renal transplant), and diabetes, among other factors, increase the risk of dissemination and occurrence of EPTB.[5] ATB may be further classified as per the pattern of infection: luminal or intestinal, peritoneal, visceral (involving solid organs like the liver, pancreas, and spleen), or lymph nodal.[6] The present review will discuss the recent advances in the field of ATB, predominantly focussing on intestinal and peritoneal TB.

ABDOMINAL TUBERCULOSIS

A number of mechanisms have been reported to result in causation of gastrointestinal TB, including spread through the haematogenous route from the primary pulmonary focus, ingested mycobacteria from the sputum produced from active lung lesions, direct or contiguous spread from adjacent organs, and through the lymphatics of infected lymph nodes.[2,6] Peritoneal involvement is the most common form of ATB, seen in up to 58% of cases, followed by intestinal involvement in 40%.[7,8]

Clinical Presentation

As discussed, peritoneal TB is the most common presentation of ATB and accounts for 1.0–6.1% of all EPTB cases. Usually seen in young adults aged 20–40 years, peritoneal TB is more prevalent in women in developing countries, while in developed countries men are more commonly affected.[9,10] The usual mode of spread is reactivation of latent foci in the peritoneum, seeding by a haematogenous route, often from distant pulmonary focusses and through ingestion of bacilli and infection of mesenteric lymph nodes. Alternatively, peritoneal TB can occur through contiguous spread from infected nodes, from ileocaecal TB, or directly from the fallopian tubes, stimulating latent foci reactivation.[7,10]

Three forms of peritoneal involvement are usually described; namely, the wet ascitic type, dry adhesive type, and fibrotic fixed type with loculated ascites and omental involvement.[6] A rare presentation with overlap of the aforementioned three forms leads to adhesion and encapsulation of the bowel and an abdominal 'cocoon' formation; this distinct form of peritoneal TB presents with intestinal obstruction and mass per abdomen.[11] The clinical presentation of peritoneal tuberculosis is of insidious onset, spanning over weeks to months, and the most common symptom is abdominal pain, seen in 49–100% of cases, followed by fever in 52–76%, weight loss in 61%, constipation in 7–31%, diarrhoea in ≤4.7%, and hepatosplenomegaly in 2–8%. Physical examination reveals ascites in 35–100% of patients, abdominal tenderness in 47%, and a doughy feel to the abdomen in ≤13%.[7,9,10] Tubercular abdominal cocoon presents with intestinal obstruction in 73.3% and a lump in 60% of cases, and has previously been treated with surgical intervention, but a recent report describes a successful conservative management with anti-tubercular therapy (ATT) in the majority of the study cases.[11,12]

Intestinal TB (ITB) is grossly classified as ulcerative, hypertrophic, ulcerohypertrophic, and fibrotic (stricturing). The ileocaecal region is the most common location involved, affecting 44–93% of cases due to the relatively narrow lumen, stasis, and abundant lymphatics.[5] The second most common location is the colon, while the stomach and oesophagus are rarely involved. Regardless of the site involved, presentation of abdominal pain, weight loss, fever, and features of intestinal obstruction are observed. Diarrhoea is uncommon but may occur with the ulcerative form of ITB.[5,13-20] In addition to abdominal pain, colonic TB may cause rectal bleeding as one of the dominant symptoms, and occasionally the bleeding may be massive.[6]

Differential Diagnosis

The closest differential diagnosis of tuberculous peritonitis is peritoneal carcinomatosis. These conditions can be differentiated by ascitic fluid analysis, where cytology will be positive for malignant cells with high protein and low gradient ascites.[21] Imaging can also help to differentiate, with computed tomography (CT) showing low attenuation mucinous ascites with amorphous calcifications scalloping the margins of the liver and spleen; however, no imaging finding is conclusive for discrimination of these entities.[22] In patients presenting with intestinal obstruction, there is a possibility of extraluminal causes such as adhesions, masses (appendicitis, diverticulitis, peritoneal carcinomatosis, neuroendocrine tumour, lymphoma), strangulation, hernia, and malrotation. Alternatively, intraluminal causes like Crohn's disease (CD), intussusception, radiation enteropathy, bezoars, and malignant masses need to be considered. Peritoneal carcinomatosis has similar imaging features like abdominal cocoon; namely, internal hernia, pseudomyxoma peritonei, peritoneal carcinomatosis, peritoneal mesothelioma, sclerosing malignant lymphoma, and malignant primary mesenteric tumours.[23-25]

Diagnosis of Abdominal Tuberculosis

The diagnosis of EPTB, especially ATB, is difficult to establish, with the primary reason for this being the low positivity of microbiological tests in this setting. Paustian's criteria suggest that the diagnosis be established if any one of the following four criteria are observed: histology showing tubercles with caseating necrosis, suggestive operative findings and consistent histology from mesenteric lymph nodes, animal inoculation or culture showing growth of *Mycobacterium tuberculosis,* or histology showing acid-fast *bacilli* in the lesion.[26] However, Paustian's criteria are difficult to establish in most cases and Logan's modification of the Paustian's criteria, which uses response to ATT, has often been used to establish the diagnosis.[27] On the other hand, the appropriate time and manner of establishing an adequate response to ATT has remained unclear. The investigational modalities for the diagnosis of ATB include radiological, biochemical, histology or cytology, and microbiological, including molecular tests and ancillary or supportive tests. Certain tests like chest roentgenogram and Mantoux skin test may have ancillary value but cannot be used as standalone diagnostic tools. Chest X-ray may be able to detect active or past evidence of pulmonary TB and thereby provide corroborative evidence of ATB; such changes may be detectable in a quarter of the patients.[6] Mantoux test (tuberculin or purified protein derivative test), in particular, is compromised by false-positive (underlying Bacillus Calmette–Guérin vaccination, cross-reaction with other mycobacteria) and false-negative (disseminated TB, immunosuppression, recent infection, extremes of age). Interferon gamma release assays (IGRA) may overcome some limitations of Mantoux testing and do not have cross reactivity with Bacillus Calmette–Guérin or other mycobacteria; however, their positivity is consistent with *M. tuberculosis* infection but cannot be used to diagnose active disease.[28] HIV testing should be performed in all patients suspected to have ATB.

INVESTIGATIONS

Radiological Evaluation

Radiological findings in patients with ATB may help in localising the site of involvement and directing further evaluation; however, no radiological finding is diagnostic of TB. Although barium studies were used frequently in the past, CT now provides the ability to identify intraluminal and extramural abnormalities and has replaced the use of barium studies.[29] Findings supportive of a diagnosis include the presence of ascites, peritoneal thickening and enhancement, omental nodularity or thickening, lymphadenopathy, mural enhancement and thickening of the bowel wall, and intestinal strictures, as well as others (Figure 1). The presence of pulmonary lesions, a hypodense centre in an enlarged lymph node suggesting necrosis, and ascites are considered highly suggestive of TB (when discriminating from CD).[30] CT enterography may have value over traditional contrast-enhanced CT, especially for better delineation of strictures.[29] Tubercular strictures are usually short, smooth, and concentric; however, discrimination from other lesions, including fungal infections and malignant lesions of the peritoneal and intestine, requires histological evidence. A recent paper that compared the use of magnetic resonance enterography with small bowel follow-through suggested that magnetic resonance enterography diagnosed a higher number of strictures except when used in the evaluation of extraintestinal lesions.[31]

Diagnostic Evaluation for Peritoneal Tuberculosis

The utility of ascitic adenosine deaminase measurement for the diagnosis of peritoneal TB has been confirmed by systematic reviews.[32,33] Adenosine deaminase is an enzyme secreted by activated lymphocytes and a value of >39 U/L in the ascites is indicative of a diagnosis of peritoneal TB.[34] Since the positivity of microbiological tests, including smear for acid-fast *bacilli* and culture for TB, is exceedingly low, clinicians have to depend on the adenosine deaminase test to a large extent. However, the test may suffer from high false-negative rates, especially in the setting of underlying cirrhosis.[35] Other findings on ascitic fluid analysis, which are consistent with a diagnosis of tubercular peritonitis, show a straw-coloured fluid, lymphocyte predominant cytology, high protein values, and low serum ascites albumin gradient.[7] Sensitivity of polymerase chain reaction (PCR)-based tests is expected to be low and has been demonstrated by some studies; however, a positive test on peritoneal fluid is specific for the diagnosis.[36] Needless to say, any diagnosis of peritoneal TB on the basis of this test must be established only after exclusion of other differential diagnoses, including peritoneal carcinomatosis by three cytological evaluations for malignant cells. Peritoneoscopy may need to be used in some cases and can show tubercles, thickened peritoneum, and adhesions.[37]

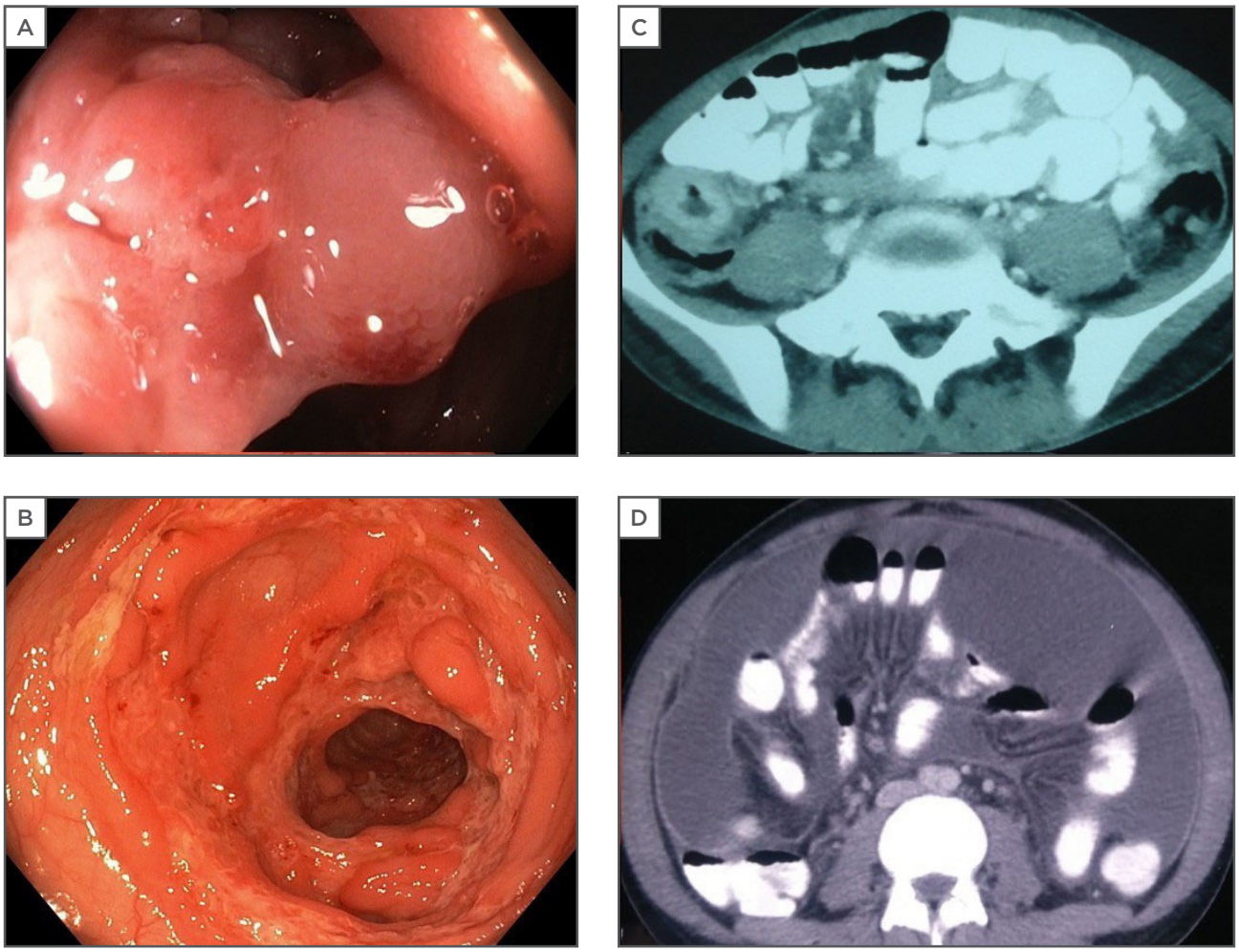

Figure 1: Radiological and endoscopic findings in abdominal tuberculosis.
A: colonoscopic image showing narrowed, thickened ileocaecal valve; B: circumferential colonic ulcers; C: thickened caecal wall on CT; D: CT showing ascites with peritoneal enhancement.
CT: computed tomography.

Diagnostic Evaluation for Intestinal Tuberculosis

Colonoscopy is the most important tool for evaluation of ITB as it helps in the characterisation of lesions, as well as in obtaining samples for microbiological and histological analysis. The colonoscopic findings in ITB include intestinal ulcers (usually transverse), pseudopolyps, strictures (usually short), and involvement of the ileocaecal valve (Figure 1). However, none of these are pathognomonic of TB and may be found in other conditions, including CD. The histological or cytological diagnosis is often based on fine-needle aspiration or biopsy obtained from radiology-guided sampling of the abdominal lymph nodes, peritoneal or omental thickening, or on endoscopic biopsies from the involved intestinal segments. The features suggestive of TB include the presence of granulomas, giant cells, caseating necrosis, and demonstration of acid-fast *bacilli*. The presence of granulomas is not unique to TB and may occur in other lesions, especially CD, fungal infections, and sarcoidosis; the presence of caseating necrosis is deemed to provide some degree of specificity to the diagnosis. Discrimination from CD is difficult, but the presence of multiple, large, confluent granulomas may be discriminative for TB. However, granulomas are only detected in a minority of cases (20–50%).[38]

Microbiological tools for the diagnosis include smear and culture for acid-fast *bacilli* and PCR-based tests; the low yield from the peritoneal fluid and intestinal biopsy samples is the Achilles' heel of microbiological tests. The culture for TB and mycobacterium growth indicator tube (MGIT)-960 (Becton, Dickinson and Company, Franklin Lakes, New Jersey, USA) is unlikely to be positive in >50% of the cases.[39,40] The use of PCR-based tests has

been reported in multiple studies; a report on the use of multiplex PCR (using three probes: 16S rRNA, IS6110, and devR) provided excellent sensitivity for the diagnosis of both peritoneal and ITB but the findings await validation.[41] Although the Xpert® MTB/Rif has emerged as an important tool for the diagnosis of pulmonary TB and some forms of EPTB (lymphadenitis), the reports on the use for ATB have indicated a limited benefit.[42,43] In a report on the use of Xpert in peritoneal TB, the test was positive in only 4 out of 21 patients who were diagnosed with peritoneal TB.[42] Similarly, in a report on ITB, only 3 out of 37 patients had a positive Xpert MTB/Rif test, suggesting that the sensitivity of the test for ATB would be low.[43] In another study, the positivity of Xpert was reported to be lower than MGIT-960 for peritoneal TB (17.9% versus 25.5%). The yield of an in-house PCR (using three genes: *hsp-66*, *esat-6*, and *ITS MAC*) was also reported to be low.[44] The bulk of evidence therefore suggests that, like other microbiological tools, PCR-based tests also provide a low sensitivity for the diagnosis of ATB.

A therapeutic trial of ATT can also be used in the diagnosis and discrimination of ATB from other conditions. A recent study from India has shown that endoscopic healing of ulcers in patients started on empirical ATT may allow differentiation of ITB from CD.[45] While the global symptomatic response with ATT was 38% and 37% in patients with CD at 3 and 6 months, respectively, 94% and 99% of patients with ITB showed a response at 3 and 6 months, respectively. When endoscopic response was observed at the end of ATT, all ITB patients had mucosal healing, while only 5% of CD patients showed mucosal healing; similar findings were also documented in the validation cohort. Therefore, persistent symptoms after 3 months of ATT may indicate a diagnosis of CD; however, the presence of a clinical response to ATT does not exclude the possibility of CD and mucosal healing should be sought.[45] Furthermore, a recent study has shown that a lack of decline in C-reactive protein levels in patients on treatment with ATT may suggest alternative diagnosis.[46]

Table 1: Differences between Crohn's disease and intestinal tuberculosis.

Parameters	CD	ITB
Duration	Long	Shorter
Clinical features	Chronic diarrhoea Haematochezia Perianal disease Extraintestinal manifestations Oral ulcers	Fever Ascites Pulmonary involvement
Site of involvement	Left colon (rectal) Multiple colonic segments	Right colon (caecal) Lesser number of colonic segments (<4)
Endoscopic appearance	Longitudinal serpiginous ulcers, aphthous ulcers Mucosal bridge Pseudopolyps and cobblestoning	Transverse ulcers Patulous ileocaecal valve
Histologic features	Focally enhanced colitis	Caseation necrosis* Confluent and submucosal granuloma Lymphocyte cuffing Ulcer lined by histiocytes
Radiologic features	Comb sign Skip lesions Intestinal mural stratification Fibrofatty proliferation Eccentric stricture	Pulmonary infiltrates or fibrosis Ascites Abdominal lymphadenopathy (>1 cm and with hypodense centre*) Short segment involvement Concentric short strictures
Laboratory and serological markers	Positive ASCA	PCR positivity for IS6110* Positive IGRA
Treatment-related factors	Recurrence after surgery	Endoscopic response to ATT with ulcer healing*

*Findings highly specific for diagnosis of ITB.

ASCA: anti-*Sacchromyces cerevisae* antibodies; ATT: anti-tubercular therapy; CD: Crohn's disease; IGRA: interferon gamma release assay; ITB: intestinal tuberculosis; PCR: polymerase chain reaction.

Another concern in the management of ATB is drug resistance and, therefore, the knock-on effect in patients with HIV, those with a previous history of ATT, and those not improving on treatment should be considered and cultures for drug sensitivity must be done.

INTESTINAL TUBERCULOSIS OR CROHN'S DISEASE: HOW TO DIFFERENTIATE?

In countries where ITB is more prevalent, CD is being increasingly recognised.[47-50] Both these chronic granulomatous disorders have similar clinical, endoscopic, radiologic, and histologic pictures; however, the natural history of both these disorders is strikingly different with serious implications regarding management. Misdiagnosis of one disease as another may be associated with multiple problems, including unnecessary immune suppression, drug toxicity, and delay in appropriate treatment. Table 1 shows important parameters used to differentiate CD from ITB.[50-54] In one study, the presence of longitudinal or aphthous ulcers, anorectal lesions, and cobblestoning favoured CD, while transverse ulcers, patulous ileocaecal valve, <4 segments involved, and scars or pseudopolyps favoured ITB.[55] Addition of CT enterography to colonoscopy increases the diagnostic accuracy and ability to differentiate CD from ITB from 66.7% to 95.2%. In a recent systematic meta-analysis of 38 studies, including 2,117 CD and 1,589 ITB patients, variables with significant odds ratios and low heterogeneity were selected to build a Bayesian model incorporating pre-test probability and diagnostic likelihood ratios to estimate probability of CD and ITB depending on local prevalence.[56] Features favouring CD were reported to be male sex, blood in stools, perianal lesions, bowel obstruction, extraintestinal manifestations, longitudinal ulcers on colonoscopy, cobblestone pattern, stricture, mucosal bridging, and rectal involvement. Histology suggesting focally enhanced colitis and CT findings of asymmetrical mural thickening, mural stratification, comb sign, and proliferation of the fibrofatty tissue also indicate the presence of CD. The findings that favoured the diagnosis of ITB were pyrexia, night sweats, pulmonary involvement, ascites, transverse ulcers, patulous ileocaecal valve, and caecal involvement on colonoscopy. Histological findings of submucosal granulomas or confluent granulomas, lymphocyte cuffing, and histiocyte lined ulcers, CT findings of short segmental involvement, and a positive IGRA also favour ITB diagnosis.[56]

Though differentiation has been validated in a local cohort from Bangkok, Thailand, with high diagnostic accuracy, the results need to be validated further in several local populations across countries with high prevalence of CD and ITB to prove its strength.[56] A recent systematic review and meta-analysis of studies looking at the accuracy of CT features in differentiating ITB from CD involving six studies with 417 and 195 patients of CD and ITB, respectively, has shown that a comb sign and necrotic lymph nodes are features with the best diagnostic accuracy to differentiate CD and ITB.[30] A further meta-analysis involving nine studies, with 340 CD and 369 ITB patients, has shown that PCR for *M. tuberculosis* has a high specificity for distinguishing ITB from CD; however, due to a very low sensitivity, a negative result does not completely rule out the diagnosis of ITB.[57] Finally, a systematic review and meta-analysis involving 11 studies with 1,081 patients with CD or ITB has shown a high specificity of IGRA and anti-*Saccharomyces cerevisiae* antibody for the diagnosis of ITB, with a supplementary role of distinguishing ITB from CD.[58] However, the results from the Indian studies are not encouraging. In addition, faecal TB PCR for IS6110 specific for *M. tuberculosis* may help discriminate ITB from CD.[59]

TREATMENT OF ABDOMINAL TUBERCULOSIS

Treatment of ATB, as with other forms of EPTB, is challenging. The challenges a clinician encounters include determining the appropriate duration of treatment, criteria to determine appropriate response to treatment, determining the end points of treatment, and recognition and treatment of sequel of ATB. The question regarding the appropriate duration of therapy has been addressed by multiple randomised trials, and a Cochrane review on the issue.[60,61] The systematic review of the three included trials, involving 328 participants, suggests that 6 months of treatment (with isoniazid, rifampicin, pyrazinamide, and ethambutol) is adequate in patients with ATB (primarily intestinal and peritoneal).[61] The included trials did not involve patients with HIV or comorbidities, or those who had received ATT previously as well as those with other forms of ATB (e.g., hepatic and pancreatic) and therefore the results may not be applicable to these patients.

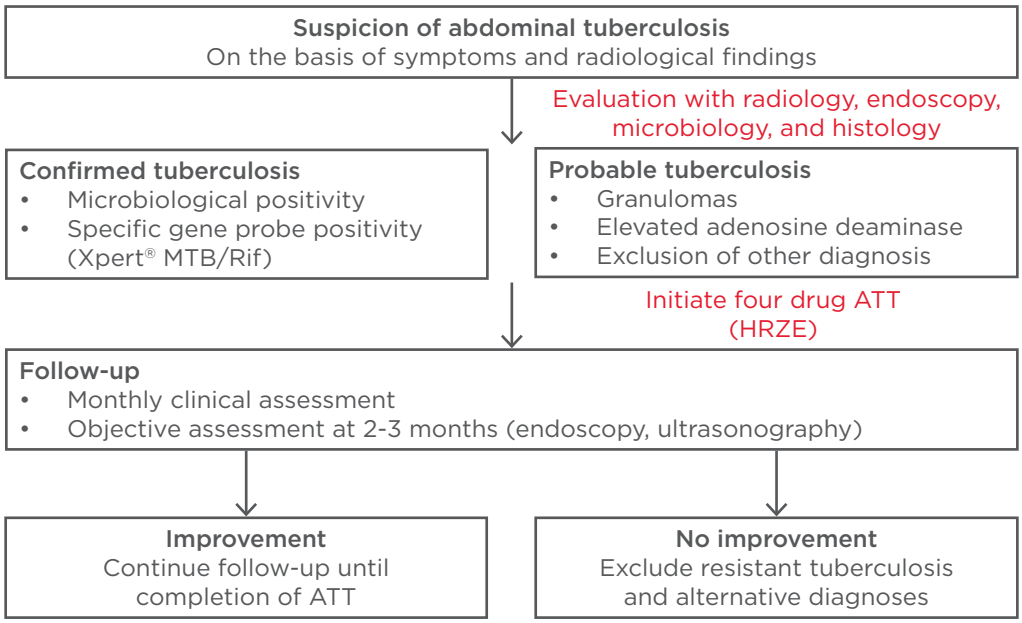

Figure 2: Suggested follow-up of patients with abdominal tuberculosis.
ATT: anti-tubercular therapy; HRZE: isoniazid, rifampicin, pyrazinamide, and ethambutol.

The appropriate method of follow-up of patients with ATB is a challenging issue. Even though the disease may heal, persistence of symptoms may be related to sequelae like peritoneal adhesions or intestinal strictures. Continued symptoms may result in an unwarranted prolongation of treatment. Therefore, the follow-up should include both objective and subjective parameters for assessment of response. For ITB, demonstration of endoscopic healing (especially the ulcers) appears to be an excellent method to document response and may be performed at 2–3 months or later (Figure 2). A recent paper demonstrated the use of this approach to discriminate ITB from CD in patients where a therapeutic trial of ATT was administered in indeterminate lesions.[45] In cases of non-healing ulcers, the possibility of drug-resistant TB or an alternative diagnosis must be considered; the frequency of drug-resistant TB varies from one geographic location to another but culture and drug sensitivity should be performed in patients with non-healing mucosal lesions or at the initial evaluation in those with previous history of ATT therapy or patients with HIV.[62] While an important concern in western India, drug-resistant TB is uncommon in patients with ATB reported in north India and South Korea.[43,62,63] For the follow-up of patients with peritoneal TB, abdominal ultrasonography to look for resolution of ascites could be an appropriate strategy (Figure 1). Other parameters that are often used to assess response include improvement in appetite and general wellbeing, defervesce of fever, and weight gain. A recent paper also suggests that patients with the special form of peritoneal TB, abdominal cocoon, may also benefit from a conservative approach with ATT and the majority of patients can therefore avoid surgery.[11] In a recent multicentre Indian study, the treatment completion rates for ATB were lower than most other forms of EPTB (like pleural, lymph-nodal, genitourinary) although the reasons for this are not clear.[4]

A recent study noted that while symptom resolution occurs in half of the patients, stricture resolution was noted only in a quarter of the patients. Furthermore, colonic stricture was more likely to persist and therefore endoscopic or surgical treatment may be needed for symptomatic patients.[64] Possible reasons for surgical intervention could include perforation, gastrointestinal bleeding, unremitting or recurrent intestinal obstruction due to intestinal strictures, adhesions, and cocoon, as well as others. In a recent series of 756 patients with ATB seen over a period of 20 years, a third of the cases needed surgery; however, this may be a biased figure since the data are from a surgical unit.[65] Other reports suggest that a subset of the patients will need surgery.[66] Acute presentation in the form of intestinal perforation or unremitting intestinal obstruction warrants surgical intervention. However, in cases where the strictures are amenable to endoscopic

dilatation (short, endoscopically reachable), endoscopic dilatation may help avoid surgery.[67]

CONCLUSION

To conclude, ATB remains an important concern in developing countries. The discrimination of ITB from CD is challenging and often necessitates a trial of ATT. ATT therapy for 6 months is usually adequate for mucosal healing and resolution of ascites, but sequelae like intestinal strictures may result in persistent symptoms needing endoscopic dilatation or surgical intervention.

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EXTRAGASTRIC GASTROINTESTINAL MANIFESTATIONS OF *HELICOBACTER PYLORI*: FRIEND OR FOE?

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ABSTRACT

Since it was first identified in 1982, *Helicobacter pylori* has continued to draw attention far beyond its role in peptic ulcer disease and is now associated with a myriad of immune-mediated diseases, both inside the gastrointestinal tract (GIT), such as mucosa-associated lymphoid tissue lymphoma, and systemic diseases, such as *H. pylori*-associated immune thrombocytopenia. This association has ignited research into the mechanisms of *H. pylori* pathogenicity, especially regarding its role within a multitude of diseases outside the GIT. Despite controversies, a growing body of evidence has begun to establish potential associations between *H. pylori* and extragastric GIT pathologies; *H. pylori* has recently been associated with luminal diseases, such as inflammatory bowel diseases and coeliac disease, as well as pancreatic, hepatobiliary, and malignant diseases of the GIT. Despite the lack of conclusive evidence regarding the mechanisms of these relationships, studies have found strong associations, like the case of *H. pylori* and coeliac disease, while others have not discovered such connections. In addition, while studies have established positive associations between *H. pylori* and various extragastric diseases, other studies have found the pathogen to play a protective role in disease development. This review comments on the latest evidence that addresses the role of *H. pylori* in non-gastric gastrointestinal diseases, and establishes the nature of these relationships and the implications of *H. pylori* eradication from a clinical perspective.

Keywords: Associations, gastrointestinal, *Helicobacter pylori,* manifestations.

INTRODUCTION

Helicobacter pylori is a curved, Gram-negative bacillus that colonises the gastric mucosa, usually during childhood, and can persist throughout the host's life without requiring intervention.[1,2] The prevalence of *H. pylori* in the adult population of north Europe and the USA is approximately 30%, compared to a higher range of 40–80% reported in adults living in or immigrating from south and east Europe, South America, and Asia.[3] Moving away from its most well-known role in gastritis and peptic ulcer diseases,[4,5] increasing evidence focusses on *H. pylori*-associated extragastric manifestations within the gastrointestinal tract (GIT).

HELICOBACTER PYLORI AND INFLAMMATORY BOWEL DISEASES

Cases of inflammatory bowel disease (IBD), consisting mostly of ulcerative colitis and Crohn's disease (CD), are immune-mediated chronic inflammatory diseases of the bowel. The exact pathogenesis of IBD is unknown; however, it is theorised to result from a dysregulated immune response to host intestinal microflora among genetically susceptible individuals.[6]

Recent data focussing on *H. pylori* involvement in the pathogenesis of IBD is gaining attention.[6-9] Various mechanisms have been proposed that link *H. pylori* to IBD, including induction of alterations in gastric and intestinal permeability via various immunological pathways, or via induction of

antigenic material absorption with subsequent loss of self-tolerance.[10] In the context of gastritis, the histopathology of the gastric mucosa infected with *H. pylori* is understood to strongly stimulate mucosal inflammation, thereby causing an inflammatory response characterised by an influx of neutrophils, mononuclear cells, and T helper 1 (Th1) cells that destroy intracellular pathogens.[4,11,12] Furthermore, *H. pylori* interaction with the gastric epithelium induces a proinflammatory response, including the recruitment and upregulation of chemokines and cytokines. However, as *H. pylori* does not exist intracellularly, the Th1 response results in endothelial damage to the host's gastric mucosa and is incapable of pathogen clearance.[13]

Several studies have reported that the prevalence of *H. pylori* infection is lower in patients with IBD compared to controls,[7,8,10,14,15] and this inverse relationship prompted investigations and shifted the focus of research to the potential protective role of *H. pylori* in the development of IBD. By colonising the gastric mucosa, *H. pylori* has acquired a series of attributes, primarily a downregulation of the host's immune system to evade both the innate and acquired immune system and prevent pathogen clearance.[4,12] While the mechanisms of proinflammatory states are linked to the development of gastritis and other inflammatory diseases, the long-term, sustained relationship between *H. pylori* and the human host raises the possibility of an existing symbiotic relationship, in which its persistence in the GIT may be beneficial to some individuals. Through these proposed mechanisms, it has been suggested that *H. pylori* plays a protective role in some immune-mediated and allergic diseases.[11,12,16-18]

A meta-analysis of the prevalence of *H. pylori* among IBD patients compared to their control subjects showed a lower prevalence of *H. pylori* infection among IBD patients.[10] Another meta-analysis, including 4,400 IBD patients and 4,763 controls, resulted in a prevalence of 26.0% versus 44.7% of *H. pylori* positivity in the IBD versus control group, respectively.[19] This inverse relationship may have some alternative explanations; firstly, it has been suggested that treatment with sulfasalazine, or the long-term and wide-spectrum antibiotic therapy among IBD patients, could be responsible for the eradication of *H. pylori*.[6,20] Notwithstanding this, a recent meta-analysis found that the protective effect of *H. pylori* was not influenced by previous use of amino salicylates or corticosteroids; however, antibiotics amplified this negative association.[7] Secondly, it is possible that immunological alterations of the gut mucosa induced by IBD could prevent *H. pylori* colonisation.[8] Lastly, it has been proposed that *H. pylori* infection shifts the equilibrium between Th1 and Th2 immune responses to a Th2-dominant pattern.

In addition, since the eradication of *H. pylori* increases the levels of Th1 proinflammatory cytokines, genetically susceptible individuals are predisposed to CD.[14] With respect to Th1 and Th2 immune responses, data are limited on the prevalence of virulent *H. pylori* strains among IBD patients; however, one study showed that both CD patients and controls were equally infected by *H. pylori* seropositive for cytotoxin-associated antigen A (Cag A), demonstrating no correlation between virulent *H. pylori* strains and the risk of IBD.[6] Furthermore, Engler et al.[20] investigated the possible protective effects of *H. pylori* by administering regular doses of *H. pylori* extract into dextran sodium-sulfate-induced chronic colitis mouse models. The results demonstrated that this experimental infection with *H. pylori* in mouse models alleviated clinical and histopathological features of chronic colitis and T cell transfer-induced colitis, and proposed that *H. pylori* can be exploited for the prevention and/or treatment of IBD through its immunomodulatory activity.[18,20] Taken together, this evidence indicates that there is a relatively strong negative association between the presence of *H. pylori* and IBD, whereas direct inhibition of IBD by *H. pylori* remains to be determined in humans.

HELICOBACTER PYLORI AND MICROSCOPIC COLITIS

Microscopic colitis is an umbrella term consisting of chronic colonic inflammation characterised by a normal macroscopic appearance of the colonic mucosa, contrasted by the presence of intraepithelial lymphocytic infiltrate or subepithelial collagen bands on biopsy. The primary cause of microscopic colitis is not fully understood, but it has been suggested to be a result of an immunological reaction to luminal antigens of ileal origin.[21,22]

Current data support an inverse relationship between *H. pylori* and microscopic colitis, similar to that seen in IBD. While Sonnenberg et al.[23,24] also established a negative correlation between microscopic colitis and *H. pylori*, another potential factor was exposed. The prevalence of *H. pylori* was shown to vary among ethnic groups, which in

turn directly affected the prevalence of microscopic colitis among patients. For example, where *H. pylori* was prevalent within the Hispanic populations, there was a notable reduction in the incidence of microscopic colitis, whereas there was an increased prevalence among Caucasians and African-American populations. This inverse relationship established between *H. pylori* and microscopic colitis may shed light on the ethnic variations in *H. pylori* gastric colonisation and may be partly responsible for the observed ethnic distribution of microscopic colitis.[23,25] Research addressing the associations between *H. pylori* and microscopic colitis remains limited; to gain further insight into the precise role of *H. pylori* in microscopic colitis pathophysiology, additional research is warranted.

HELICOBACTER PYLORI AND COELIAC DISEASE

Coeliac disease, also known as gluten-sensitive enteropathy, is an autoimmune disease involving interactions between environmental, genetic, and immunologic factors; specifically, it is defined as a T cell-mediated immune disorder that is induced by gluten ingestion in genetically predisposed individuals.[26,27] There has been a significant increase in the incidence of coeliac disease in recent decades,[28] rather than those cases recorded solely as a by-product of improved and increased detection. This trend is not well understood; however, environmental factors, specifically a reduced exposure to bacteria, also known as the 'hygiene hypothesis', have been proposed to be reponsible.[29] As part of an analysis of a nationwide pathology database, Lebwhol et al.[29] found a strong inverse relationship between the presence of *H. pylori* and coeliac disease, independent of confounding factors. Although the potential protective mechanism is uncertain, this study is consistent with other studies attributing the role of *H. pylori* with a decreased risk of allergic and inflammatory conditions.[18]

In 2015, Robinson et al.[5] conducted a systematic review on the protective role of *H. pylori* against the risk of acquired autoimmune disorders. Where some studies showed that the prevalence of *H. pylori* was reduced in coeliac disease, other reports found no differences. While these controversies could be explained by research methodologies, biases, or confounders, the mechanisms by which *H. pylori* might protect against CD remain unknown. Shortly after this review, Rostami-Nejad et al.[30] reviewed a series of reports addressing pathological and clinical correlations between coeliac disease and *H. pylori* infection. A comprehensive review of research articles from 1985–2015 concluded that examinations of the correlation between *H. pylori* and CD have once again yielded discordant outcomes.[30]

More recently, Basyigit et al.[31] failed to confirm a significant relationship between coeliac disease and *H. pylori*. Serum levels of coeliac disease-specific autoantibodies or immunoglobulin A were analysed among both *H. pylori* and non-*H. pylori*-infected individuals and no significant differences in serum level antibodies were found. Conversely, Narang et al.[32] concluded that the prevalence of *H. pylori* in children with confirmed coeliac disease was lower in comparison to *H. pylori* infection rates in children without coeliac disease, signifying an inverse relationship. While protectivity has still not been confirmed, the potentiality now merits further longitudinal investigations to ascertain whether *H. pylori* infection confers protection or a reduced risk of developing coeliac disease.

HELICOBACTER PYLORI AND HEPATOBILIARY DISEASES

Early research suggests the *Helicobacter* species is implicated in hepatobiliary diseases, ranging from chronic cholecystitis and primary sclerosing cholangitis (PSC), to gallbladder and primary hepatic carcinomas (Table 1).[17,69,70] The *Helicobacter* species, including *H. pylori*, has been implicated as a potential inducer of hepatocyte and biliary autoimmunity, primarily based on their tolerance to, and ability to survive in, bile.[71]

However, *H. pylori* primarily affects the GIT and is not commonly present in the liver and bile ducts of *H. pylori*-infected individuals. Contamination of the hepatobiliary system is most likely due to contamination from potentially damaged gastrointestinal epithelium, or to the dysfunctional sphincter of the common bile duct; however, the entry of *H. pylori* through this mechanism, and the susceptibility of biliary tract contamination, is not limited to *H. pylori*. This presents challenges in the assessment and controlled research concerning the role of *H. pylori* in the development of hepatobiliary pathologies.

There is minimal evidence of association pertaining to the role of *H. pylori* in autoimmune biliary diseases, including primary biliary cirrhosis (PBC) and PSC.[33,71]

Table 1: Extragastric gastrointestinal associations of *Helicobacter pylori*.

Disease	Conclusion
Inflammatory bowel diseases[7,8,10,14,15]	Epidemiological data and meta-analysis show a negative association.
Microscopic colitis[23-25]	Epidemiological data and cohort studies indicate a positive association.
Coeliac disease[5,29,30,32]	Conflicting evidence is present.
Primary biliary cirrhosis[33-36]	No statistically significant associations found.
Primary sclerosing cholangitis[37-40]	Cohort and prospective analysis shows a positive association.
Gallstone disease[36,40-46]	Epidemiological and cohort data show a positive association.
Autoimmune hepatitis[47]	Currently lacks conclusive evidence due to limited research.
NAFLD[48-53]	Majority of data (case-control, cross-sectional, and systematic reviews) confirm a positive association of *H. pylori* infectivity and insulin resistance, predisposing patients to NAFLD.
Pancreatitis[54,55]	Majority of data confirm a positive association, including cross-sectional and cohort analysis.
Pancreatic cancer[56-62]	Majority of data suggest a positive association, including a meta-analysis, but two case-control studies found no association.
Colorectal cancer[63-68]	Systematic review and meta-analysis support the positive association.

NAFLD: non-alcoholic fatty liver disease.

As both conditions are caused by an immune-mediated cellular destruction within the biliary system, research into the implication of *H. pylori* infectivity within the pathophysiology of these diseases has recently gained attention.

Primary Biliary Cirrhosis

While certain attempts have failed to detect *H. pylori* in the livers of patients with PBC,[33] others have detected *H. pylori* in a very limited number of samples.[34] Studies, such as that by Boomkens et al.,[70] could only find the presence of *Helicobacter* species in approximately one-third of all samples tested, which suggested that PBC is unlikely to be caused or influenced by *Helicobacter* infection. Additionally, research specifically assessing Cag A seropositivity of *H. pylori* in PBC patients compared to control groups also found conflicting evidence.[33,34,71] Research on molecular mimicry between *H. pylori* and PBC-specific autoantigens identified a significant amino acid sequence similarity between the mitochondrial autoepitope region of pyruvate dehydrogenase complex E2 subunit and urease beta of *H. pylori*, without any evidence of immunological cross-reactivity. Other studies involving cross-reactive antibodies against *H. pylori* also demonstrated that *H. pylori* antigens are unlikely candidates of cross-reactive targets in molecular mimicry mechanisms in PBC, contributing further to the evidence against *H. pylori* association with PBC.[35]

Primary Sclerosing Cholangitis

In comparison to PBC cases, there was some evidence identifying a positive association between PSC and *H. pylori*. A study on *H. pylori* DNA in liver samples from PSC patients detected *H. pylori* DNA in micro-dissected hilar biliary epithelium in a higher number of PSC patients compared to controls.[35] This supports the hypothesis that bile reflux, or translocation from the duodenum into the biliary tract, might transport *H. pylori* organisms into the biliary system, contributing to PSC development. Gut translocation of pathogens has been suggested among several studies as a plausible mechanism for the induction of hepatobiliary autoimmunity within the context of *H. pylori* involvement in hepatobiliary pathology.[37,39,71] Although several studies assessing the prevalence of anti-*H. pylori* antibodies in PSC patients found that titres did not differ significantly between PSC patients and control groups, it has been hypothesised that, since many PSC patients suffer from ulcerative colitis, *H. pylori* could account for any documented associations.[36-38] Thus far, a positive association between *H. pylori* and PSC has been elucidated; however, the attempts made to uncover any potential association between *H. pylori* and PSC have been limited, thereby requiring further clarification.

Gallstone Diseases

H. pylori is positively associated with cholestatic conditions, albeit with limited evidence.[34,38]

It has been proposed that *H. pylori* plays a role in the formation of cholesterol gallstones, and consequentially chronic cholecystitis.[39] For example, Attaallah et al.[41] found 37% of patients with symptomatic gallstone disease were locally infected with *H. pylori.* Other studies also found *H. pylori* to be a predisposing factor and showed that it may have a pertinent role within the aetiology and pathophysiology of gallstone formation;[40,42-44] no evidence was found for any negative or non-association in our literature review. Although causality is uncertain at this point, *H. pylori* plays a role in gallstone pathogenesis, either directly or as a potential cofactor.[45]

Autoimmune Hepatitis

Although a high prevalence of *H. pylori* infection was demonstrated in patients with viral-related cirrhosis, it was not studied in cases of autoimmune hepatitis. Durazzo et al.,[46] in their attempts to establish a relationship between autoimmune hepatitis and *H. pylori*, found no association. Current data on the role of *H. pylori* in autoimmune hepatitis are limited and inconclusive.

Helicobacter Pylori and Non-Alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is regarded as a hepatic manifestation of metabolic syndrome. It is a concerning disease, not only because of its high prevalence, but also due to its potential risk of progressing to cirrhosis and hepatocellular carcinoma. The literature focussing on the association between *H. pylori* and NAFLD is conflicting; as we have established, *H. pylori* is a pathogen reported to be well associated with metabolic syndrome,[48] but whether there is a direct association with regard to NAFLD still remains unclear.[49,50]

Okushin et al.,[49] in a cross-sectional study, aimed to clarify the nature of association between NAFLD with causative background factors, including *H. pylori* infection. While BMI, serum alanine aminotransferase, and platelet count were significantly associated with NAFLD, *H. pylori* infection was not.[49] However, others have found *H. pylori* to be an independent risk factor for the development of NAFLD.[50,51] Cheng et al.,[50] in a systematic review of *H. pylori* involvement in the pathogenicity of NAFLD, revealed the possible contributory mechanisms of *H. pylori* to the disease: *H. pylori* infection causes chronic low-grade systemic inflammation, which increases the levels of inflammatory cytokines, and, through a series of pathways ultimately leading to insulin resistance, acts as a leading contributor to NAFLD.[48,50] Lastly, Tang and Kumar[53] stated that small trials examining the effect of *H. pylori* eradication have shown improvement in markers of NAFLD activity. Not only does this support a link between the two conditions, but it substantiates the potential clinical implications beyond *H. pylori* eradication in patients with NAFLD.

HELICOBACTER PYLORI AND PANCREATITIS

Pancreatitis can be of acute, chronic, and autoimmune nature, each displaying differences in pathophysiology. Acute pancreatitis is defined as an acute inflammation of the pancreas, consequentially causing a dysregulation of pancreatic enzyme activity, and the pathogenesis ranges from hereditary and behavioural, to environmental aetiologies.[16] In contrast, chronic pancreatitis is a more progressive fibro-inflammatory disease, characterised by irreversible fibrosis of the pancreatic gland,[47] and autoimmune pancreatitis (AIP) is characterised by fibrotic, lymphoplasmacytic inflammatory processes accompanied by T cell apoptosis, which contribute to pancreatic tissue destruction.[17]

The implication of *H. pylori* in the pathogenesis of AIP via an induction of autoimmunity has been a recent topic of investigation. The role of *H. pylori* in AIP has also been investigated within the context of a high prevalence of peptic ulcer disease (PUD) in patients with AIP.[16,72] Lee et al.[72] found PUD to be positively associated with severe acute pancreatitis, thereby concluding that there are implications beyond the treatment of PUD, and the condition should be considered in the management of acute pancreatitis. Another study found that *H. pylori* increases the severity of ischaemia-induced pancreatitis, as well as inducing production of proinflammatory interleukin-1β, further aggravating disturbances in the pancreatic microcirculation in acute pancreatitis.[54] Lastly, *H. pylori* may potentiate the onset of AIP due to molecular mimicry; research investigating this molecular mimicry found *H. pylori* alpha carbonic anhydrase and human carbonic anhydrase II, among other enzymes, were highly expressed in the pancreatic ductal and acinar cells, exposing the immune system to the potential of cross-reactivity.[55] While the exact mechanisms are still unknown,

molecular mimicry, proinflammatory response, and the development of *H. pylori*-induced PUD may be involved in the development of AIP.

There is a positive association between pancreatitis and *H. pylori*; the evidence against any association between the two was not found to be statistically significant. Whether this relationship is incidental, causative, or a risk factor remains to be understood. The question concerning the implications of eradication of *H. pylori* to patients with AIP, in terms of the potential benefits, is now becoming more relevant and, therefore, as we consider the increased burden of pancreatic cancer and its association with AIP, the development of an underlying link motivates further research.

HELICOBACTER PYLORI AND PANCREATIC CANCER

Pancreatic cancer is currently the fourth leading cause of cancer-related deaths worldwide and the risk factors include tobacco, smoking, diabetes, chronic pancreatitis, alcohol, and specific genetic conditions.[73] Recently, research focussing on the associations between *H. pylori* and autoimmune diseases has found conflicting evidence for *H. pylori* involvement in pancreatic cancer. Several studies have established a positive association between *H. pylori* and pancreatic cancer.[56-58] For example, Risch et al.[57] found that there is evidence for the involvement of *H. pylori*-modulated gastric acidity in the risk of pancreatic carcinoma. Additionally, the interaction of the ABO genotype and phenotype status of an individual influences the behaviour of *H. pylori* infectivity, which in turn affects gastric and pancreatic secretory function. This ultimately influences the pancreatic carcinogenicity of dietary and smoking-related N-nitrosamine exposures.[56,59] The association of ABO-product antigen and *H. pylori* is now understood to be strongly implicated in the disease aetiology of pancreatic cancer. Furthermore, a meta-analysis including 1,003 pancreatic cancer patients and 1,754 healthy controls evaluated the presence of *H. pylori* and the risk of developing pancreatic cancer. The results indicated a significant correlation between *H. pylori* and pancreatic cancer, and showed that *H. pylori* infection can increase the risk of developing pancreatic cancer.[59] With regard to Cag A seropositivity, Stolzenberg-Solomon et al.[69] found that, compared with seronegative subjects, those with *H. pylori* or Cag A+ strains were at an elevated risk of developing pancreatic cancer.

However, several other studies found no association between *H. pylori* and the development of pancreatic cancer.[60,61] Both a case-control study by de Martel et al.[61] and a meta-analysis by Xiao et al.[74] found no associations between the presence of *H. pylori* or the Cag A protein and pancreatic cancer, whereas smoking and education were associated. Due to the limited number of studies, suspected publication bias, relatively small sample size, as well as statistical heterogeneity, the need for high-quality studies to further clarify the role of *H. pylori* in pancreatic cancer still stands.

HELICOBACTER PYLORI AND COLON CANCER

Colorectal cancer is the third most common cancer worldwide, accounting for >9% of all cancer incidences.[75] Although colonic carcinogenesis is considered a multifactorial process, including a combination of environmental factors, Western dietary and social practices, as well as genetic susceptibility, the precise mechanisms of its initiation remain unknown. Given the increased incidence of colon cancer worldwide, as well as a growing interest in the involvement of *H. pylori* in gastrointestinal diseases, studies have begun to examine the relationship, or potential association, between *H. pylori* and colonic carcinogenesis.[63]

Until now, the role of *H. pylori* in the development of colorectal neoplasm remains controversial. A study that involved mice infected with *H. pylori* exhibited oncogenic properties within the colon epithelia, including an increased expression of mutations.[64] Selgrad et al.[65] found an upregulation of Cag A expression to be associated with an increased risk of colon cancer, also associating infectivity with *H. pylori* to the development of colorectal cancer. A broader and more recent study in China, based on a retrospective analysis of intestinal biopsies, revealed that interstitial metaplasia accompanied by *H. pylori* infection was significantly associated with an increased risk of adenomas, suggesting a plausible carcinogenic effect of *H. pylori*.[66] Several large-scale studies, which included data from several case-control studies, cross-sectional studies, and meta-analyses, found a similar statistically significant association between *H. pylori* and the risk of colorectal adenoma and colorectal neoplasm.[66-68] However, it still remains to be elucidated whether the induction and perpetuation of inflammatory responses, alteration of gut microflora, and release of toxins mediated by *H. pylori* can

claim causality to colorectal tumourigenesis.[76] While the evidence thus far indicates an association, rather than a proof of causality, it calls for further large-scale studies to confirm *H. pylori* as a contributor in the pathogenesis of colorectal cancer.

CONCLUSION

H. pylori is a pathogen that has continued to draw attention for decades. Thus far, despite the increasing evidence of both positive and negative associations of *H. pylori* and extragastric diseases, specifically within gastrointestinal and hepatobiliary systems, the direct role of the pathogen in the pathophysiology of the aforementioned diseases remains elusive. The main protective effect is postulated to result from the long-term interaction of *H. pylori* with the immune system, acquired in early childhood. Evidence suggesting whether *H. pylori* eradication truly reverses the immunological benefits is lacking; however, evidence regarding the benefits of eradication exists. The lack of a concise and comprehensive understanding makes the implications of *H. pylori* infectivity unclear from a clinical standpoint. Lastly, although *H. pylori* is both a friend and a foe, currently there is no evidence against treating a patient with *H. pylori* when there is a strong clinical indication for therapy.

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NON-ALCOHOLIC FATTY PANCREAS DISEASE, PANCREATIC CANCER, AND IMPACT OF ENDOSCOPIC ULTRASOUND EXAMINATION ON SCREENING AND SURVEILLANCE

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ABSTRACT

Fat accumulation in the pancreas, defined as fatty pancreas, is usually an incidental finding during transabdominal ultrasound examination. Fatty pancreas without any significant alcohol consumption is defined as non-alcoholic fatty pancreas disease. Even though its clinical impact is still largely unknown, hypothetically the disease progression could lead to chronic pancreatitis and possibly pancreatic cancer development. Recently, metabolic problems such as diabetes, central obesity, fatty liver, and dyslipidaemia have been considered important risk factors related to non-alcoholic fatty pancreas disease and pancreatic cancer; however, the exact mechanism is not yet fully understood. Early detection and screening for pancreatic cancer in clinical practice is troublesome because of the non-specific symptoms, anatomical location, accuracy of biomarkers in clinical practice, and high risk of radiation and contrast agent exposure from imaging study. Endoscopic ultrasound is still considered the best method for pancreas evaluation and for the screening and diagnosis of pancreatic cancer. However, there is still much debate regarding its cost, availability, and the training experience of the operator.

Keywords: Endoscopic ultrasound (EUS), fatty pancreas, pancreatic cancer, screening.

INTRODUCTION

Non-alcoholic fatty pancreas disease (NAFPD) is a new clinical entity where there is evidence of excessive pancreatic fat accumulation in patients without any significant alcohol consumption.[1,2] The impact of this condition is still largely unknown even though it has been postulated that fatty pancreas may lead to chronic pancreatitis and is a possible cause of pancreatic cancer. Pancreatic cancer is the most lethal cancer in the world and early detection is still difficult due to its location and non-specific symptoms.[3]

Endoscopic ultrasound (EUS) examination is the most sensitive tool for examining the pancreas in the era of modern imaging development; however, the availability, cost, and training are still debatable, especially in most developing Asian countries.[4,5] In this review, the new paradigm of NAFPD, risk factors, its clinical impact on pancreatic cancer development, and screening modalities for early detection are discussed.

NON-ALCOHOLIC FATTY PANCREAS DISEASE AND METABOLIC RISK FACTORS

Fatty infiltration in the pancreas or fatty replacement in pancreas cells are considered benign conditions. This condition was first described by Schaefer[6] in 1926 who performed a biometric study, and later by Ogilvie[7] in 1933 who studied the pancreas through autopsies; however,

the impact of this condition in clinical practice is still largely unknown.[8] The prevalence of NAFPD has been reported in the USA as well as in Asian countries as ranging from 16–35%.[9-12] Later, the term NAFPD was described in relation to obesity and metabolic syndrome. Free fatty acid (FFA) is key to insulin resistance pathogenesis; this well-known condition makes a significant contribution to most metabolic disorders, such as diabetes, hypertension, dyslipidaemia, and non-alcoholic fatty liver disease (NAFLD). There have been many studies showing that metabolic factors are strongly related to NAFPD.[13-16] Fat accumulation in the pancreas is hypothesised to be strongly related to the increase of circulating FFA, not only from the visceral adipose tissue but also predominantly from the subcutaneous adipose tissue. That is why obesity, and especially central obesity, is thought to play the biggest role in NAFPD development and its progression.[17]

A strong association between the presence of NAFLD and NAFPD has been shown in some studies.[18-20] This concomitant phenomenon could be as high as 50% in both Asian and Western countries, these conditions share the same possible pathogenesis. Studies in the Hong Kong Chinese population showed a significant correlation between NAFPD and NAFLD (odds ratio [OR]: 2.22; 95% confidence interval [CI]: 1.88-2.57; p<0.001).[18-20] A study found that there was a direct relationship between fatty pancreas and fatty liver in central obesity.[21] In patients with biopsy-proven NAFLD, the pancreatic fat was shown to correlate significantly with the severity of hepatic steatosis.[21] There is a controversial study about this finding; however, the study sample was too small.[22,23]

Other investigations revealed that there is a strong relationship between NAFPD and diabetes, even though there is no prospective study yet to explore the clear mechanism in this condition.[12,16] Wong et al.[12] found that patients with NAFPD have a higher chance of developing insulin resistance. This study also showed that obesity and hypertriglyceridaemia were independent risk factors for NAFPD (OR: 1.79 and 3.16, respectively). It has been postulated that NAFPD can precede pre-diabetes and lead to diabetes development. Even though the exact mechanism is not yet clear, the damage and fat replacement at the acinar cells could further lead to β-cell dysfunction. This fat accumulation could lead to reactive oxygen species activation, increasing oxidative stress and resulting in β-cell apoptosis.[24,25] Alternatively, another possible mechanism of fatty pancreas development is due to congenital syndromes, including cystic fibrosis, Shwachman–Diamond syndrome, Johanson–Blizzard syndrome, and heterozygous carboxyl-ester-lipase mutations.[1]

Detection of pancreatic steatosis is challenging in clinical practice, since it is usually an incidental finding during transabdominal ultrasound. The diagnosis of fatty pancreas is based on ultrasound imaging that shows diffuse hyperechoic parenchyma when compared to the kidney. Its retroperitoneal anatomical location makes the pancreas more difficult to visualise, especially in overweight or obese patients. Some imaging modalities have been used to quantify the fat content, such as magnetic resonance imaging (MRI), since this modality can identify more accurate fat infiltration. However, transabdominal ultrasound is still easier to use without any risk of radiation or contrast agent.[2]

PANCREATIC CANCER, RISK FACTORS, SCREENING, AND EARLY DETECTION

Pancreatic cancer is still the most lethal cancer in the world, and it has a very poor prognosis. Most patients with pancreatic cancer present at a late stage of the disease because it is still difficult to detect in the earlier stages of cancer development.[26] Smoking, chronic pancreatitis, diabetes, and heavy alcohol consumption are the most common risk factors for pancreatic cancer development. However, obesity and metabolic syndrome are also considered to be important risk factors for pancreatic cancer development even though the exact mechanism requires further study. There are several pathways that explain the role of metabolic syndrome and cancer development, such as insulin-like growth factor-1 (IGF-1) pathway, hyperinsulinaemia, insulin resistance, and impact of hyperglycaemia. Evidence from colon cancer cases show a strong correlation between overexpression of IGF-1 receptors and apoptosis resistance cancer cells. In diabetes or metabolic syndrome patients, the levels of IGF-1 are decreased. Other conditions, such as insulin resistance and advanced glycation end-products due to hyperglycaemia, are also related to more advanced cancer.[27,28] The phenomenon can be explained based on interaction between factors.

The pancreas is composed of endocrine and exocrine cells. Most pancreatic cancers, originate from the exocrine gland; ductal adenocarcinoma

is the most common type. The acinar cells injury is initiated by fat replacement when there is high FFA released by peripheral adipose tissue. The excess fat replacement will worsen the fatty pancreas condition. High FFA, especially in obese patients, will also cause an imbalance of adipocytokines and lead to inflammation. Fatty pancreas or pancreatic steatosis has been hypothesised to have a similar mechanism with the spectrum of NAFLD. It has been postulated that oxidative stress can arise from long-standing fat accumulation, which leads to proinflammatory cytokine release. Chronic fat accumulation in the pancreas with chronic inflammation may lead to chronic pancreatitis and, possibly, to cancer development.[17]

Screening early pancreatic cancer is another challenge in clinical practice. Most pancreatic cancer symptoms are non-specific; the most common symptoms are dyspepsia, back pain, abdominal pain, bloating, changes in bowel habit, lethargy, and weight loss. It is important to have an accurate tool for screening and detection during the very early stages of the disease. There are biomarkers and imaging techniques that are usually used for early detection and screening. The most common marker used to detect pancreatic cancer development is CA 19-9. However, the wide range of sensitivity and specificity (68–91%) means this marker is not ideal for clinical use; additionally, high levels of CA 19-9 can also be found in several other conditions, such as cholangitis, gastrointestinal cancer, and biliary cancer, which could potentially result in misdiagnosis.[29] Other biomarkers, including *CEACAM1*, *MMP-7*, TIMP-1, and *MUC1*, have been studied; however, even though some of these markers showed better accuracy in cancer detection when combined with the older screening mechanisms, CA 19-9 is still considered inadequate, especially due to genetic heterogeneity. Another study[29] looking at a combination of CA 19-9, albumin, and IGF-1 showed that this combination could differentiate between chronic pancreatitis and pancreatic cancer with a sensitivity and specificity >90%. The major drawback is that the training set of the biomarkers may not be valid due to a higher level of collected samples. A novel biomarker study,[30] based on a microRNA assay, has also been carried out.[29,30] However, there is a controversial issue regarding the removal of pancreatic juice through invasive procedures, such as endoscopic retrograde cholangiopancreatography. microRNA has been used for plasma examination; however, a challenge with this detection method is ensuring diagnostic accuracy. To ensure the accuracy of this method before it is used in routine clinical examination, it should be validated in a large cohort. Imaging techniques, such as multi-detector helical computed tomography (CT) scan and MRI, have shown good diagnostic accuracy in the detection of pancreatic cancer. The sensitivity and specificity ranged from 80% to >90%.[30] However, the radiation exposure and contrast agent issues mean a regular CT scan is not the preferred option for routine screening and detection. Imaging techniques such as magnetic resonance cholangiopancreatography could provide useful information about early pancreatic changes, but the patient's co-operation during examination and the time needed for each examination makes this technique uncomfortable for most of the patients, especially elderly patients.[31]

ENDOSCOPIC ULTRASOUND AND ITS IMPACT IN PANCREATIC CANCER SCREENING AND SURVEILLANCE

In the diagnostic development era, endoscopic ultrasound (EUS) is known as the most sensitive method for the pancreas and biliary system. This tool has been introduced in 1980 and mostly used for diagnostic purposes only. Recently EUS has been used not only for diagnostic but also for interventional (such as fine needle aspiration [FNA]) and therapeutic purpose (such as EUS pancreatic pseudocyst drainage, EUS celiac axis block, and EUS biliary drainage).[4,32]

Pancreatic cancer screening and high pancreatic risk lesion surveillance has become a big topic for debate. The high-risk individuals are persons who have a strong family history of pancreatic cancer, especially in two or more first-degree relatives, other inherited conditions such as familial adenomatous polyps, *HNPCC*, *BRCA1* carrier, hereditary pancreatitis, and cystic fibrosis. Patients with familial atypical multiple mole melanoma (FAMM) and Peutz–Jeghers syndrome also part of the high-risk individuals. The poor survival rate and the lack of significant increase in success rate in pancreatic cancer even after surgery (only 10–20% for 5-year survival rate) makes improving diagnostic efforts a vital endeavour. The small percentage increase of pancreatic cancer incidence every year results in the current screening programmes losing cost-effectiveness. Currently, however, screening in the early stages of the disease and finding the advanced stage (including involvement of lymph node and vascular invasion) remain the only hope for longer survival

achievement. Detection of high-risk lesions may be more useful since surgery can be done in the very early stage of the disease. A study by Brentnall et al.[33] in 14 patients showed that EUS has an important role in diagnosing some abnormalities that could not detected by CT scan or MRI. Surgery results revealed dysplasia lesions in some of the patients who were previously highlighted by EUS procedures. Another screening and surveillance study[34] for pancreatic cancer detection in some family members of patients with high risk factors, such as *HNPCC*, FAMM, and Peutz–Jeghers syndrome, found that some of these patients' family members suffered from pancreatic cancer.

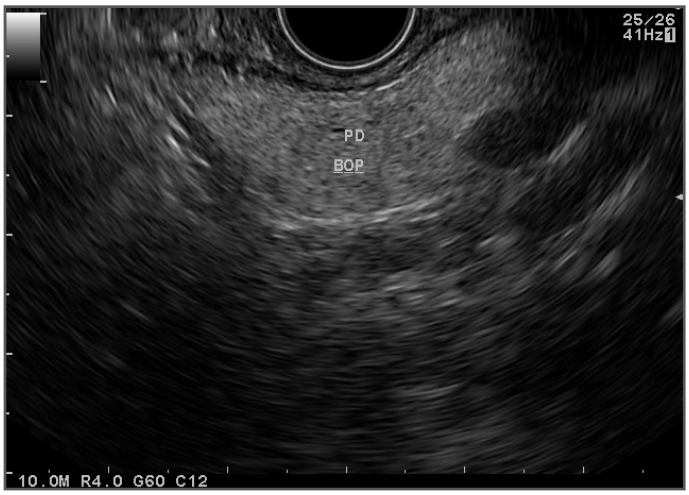

Figure 1: Endoscopic ultrasound image showing bright hyperechoic of pancreas parenchyma.

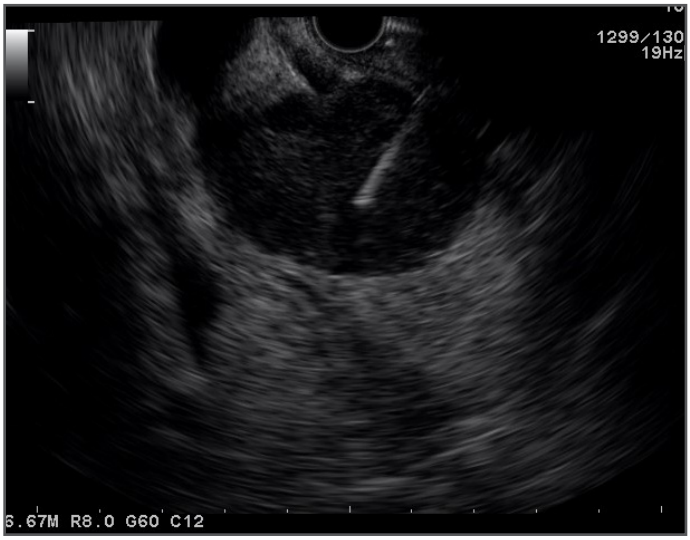

Figure 2: Endoscopic ultrasound image showing a fine needle aspiration performed in a pancreatic head mass.

The imaging studies, such as CT scan, MRI, and even positron emission tomography could not detect any abnormalities in these pancreatic cancer patients; however, they were detected by EUS examination.[34] This issue has also been proven by some studies where EUS was performed in high-risk patient groups and when detecting high-risk lesions or possible precursor lesions in patients that underwent surgery. After surgery, significantly longer survival was achieved (disease free >5 years); however, it is important to note the small sample size used in these studies.[35,36] The main problem in real-world clinical practice is that no symptoms are present in pancreatic cancer lesion <1 cm and most patients come with painless jaundice or biliary obstruction which is a sign of advance disease.[37]

Compared to other imaging modalities, the close range of pancreas examination from the stomach makes EUS the most accurate imaging modality (80–90%) even though it is still operator dependent (Figure 1).[38] The EUS-FNA (Figure 2) technique enables 'one-stop shopping', where biopsy of the suspicious nodule can be performed at the same time as screening; furthermore, EUS-FNA has been proven to have high diagnostic accuracy (>90%).[39] This method has overcome the old method of endoscopic retrograde cholangiopancreatography to do a biopsy or brush cytology. Another advantage of using EUS is that it can detect smaller (<2 cm) lesions more accurately than CT scan or MRI.[40] A systematic review[41] comparing EUS with CT scan examination in pancreatic mass detection showed the superiority of EUS over CT scan (Table 1). However, MRI can detect small cysts accurately, meaning the combination of EUS and MRI has become the main option in screening precursor lesion.[40,41] Recently, most of the cystic lesions in the pancreas can be clearly evaluated by EUS examination, especially for intraductal papillary mucinous neoplasm and mucinous cystic neoplasm. The carcinoembryonic antigen from the cystic fluid can also be an important marker to predict high-risk cystic lesions. However, since most cystic lesions do not progress to malignant lesions, the routine use of EUS screening is being debated, especially regarding the cost, training to carry out the process, and the invasiveness of the procedure. Another difficult problem with EUS is diagnosing possible malignancy in patients with chronic pancreatitis, diffusely infiltrating cancer, and recent acute pancreatitis.

Table 1: Impact of endoscopic ultrasound study on pancreatic cancer detection.

Study	Design	No. of patients or studies	Outcome
Brentnall et al.[33]	Case series in high-risk individuals	14 patients with abnormal EUS	7 patients with dysplasia from Whipple surgery results
Canto et al.[35]	EUS screening prospective study in high-risk individuals	29 patients with abnormal EUS	Pancreatic neoplasia in 7 patients who underwent Whipple surgery based on EUS study
Dewitt et al.[41]	A systematic review	11 studies	EUS is superior to CT scan examination for detection and staging

CT: computed tomography; EUS: endoscopic ultrasound.

The novel technology, EUS elastography, is a promising tool for detecting pancreatic mass more accurately than conventional EUS because it can give a better visualisation of tissue elasticity so it can target the lesion by avoiding less fibrotic areas.[42,43] Transabdominal ultrasound may be more simple, comfortable, and cost-effective for most of the patients; however, the anatomical location and the patient's preparation and condition can make the process difficult to assess.[44]

CONCLUSION

NAFPD is a new emerging disease that is an important risk factor for pancreatic cancer development. The role of EUS in early detection and screening surveillance has given a new insight into the field of gastroenterology. Patients with high-risk factors, such as *HNPCC*, FAMM, and Peutz–Jeghers syndrome, and their family members should be strongly recommended to undergo EUS screening and surveillance. Patients with metabolic risk factors, such as NAFLD, diabetes, obesity, and dyslipidaemia, might be considered for early screening examination. However, the risk-benefit ratio should always be the main consideration in clinical practice.

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ATROPHIC BODY GASTRITIS: CLINICAL PRESENTATION, DIAGNOSIS, AND OUTCOME

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ABSTRACT

Atrophic body gastritis is a chronic disorder characterised by atrophy of the oxyntic glands leading to reduced gastric acid and intrinsic factor secretion. Serological studies reported yearly prevalence and incidence rates between 3–9% and 0–11%, respectively. In atrophic body gastritis, the presence of parietal cells and/or intrinsic factor autoantibodies, and autoimmune diseases, such as autoimmune thyroid disease or Type 1 diabetes mellitus, are often observed. These cases are often diagnosed as autoimmune gastritis. This association has been included as part of the autoimmune polyendocrine syndrome. A frequent clinical presentation of atrophic body gastritis is pernicious anaemia, considered an autoimmune condition, arising from vitamin B12 malabsorption as a consequence of intrinsic factor deficiency. Another presentation may be an otherwise unexplained iron deficiency anaemia, as a result of iron malabsorption and consequence of reduced gastric acid secretion. To date, no universally accepted criteria are available to define autoimmune gastritis and to distinguish this clinical entity from chronic, *Helicobacter pylori*-driven, multifocal atrophic gastritis. In contrast with the classical perception of a silent condition, patients with atrophic body gastritis may complain of a spectrum of gastrointestinal symptoms, ranging from dyspepsia as early satiety, postprandial fullness, and epigastric pain, to gastro-oesophageal reflux symptoms such as regurgitation and heartburn. The timely diagnosis of atrophic body gastritis is important, as this condition puts patients at an increased risk of gastric cancer and other Type 1 carcinoids that may lead to micronutrient deficiencies crucial for erythropoiesis. The present review provides an update on epidemiological and clinical aspects as well as diagnosis and outcome of the disease.

Keywords: Atrophic body gastritis (AG), autoimmune gastritis, gastric cancer (GC), intestinal metaplasia (IM), pernicious anaemia (PA), Type 1 gastric carcinoids.

EPIDEMIOLOGY AND CLINICAL PRESENTATION OF ATROPHIC BODY GASTRITIS

Atrophic body gastritis (AG) is a chronic disorder characterised by atrophy of the oxyntic glands, which leads to lack of gastric acid and intrinsic factor production, often leading to micronutrient deficiencies, such as malabsorption of vitamin B12 or iron, and consequent anaemia.[1] This condition may arise from long-standing *Helicobacter pylori* infection or in the context of autoimmune gastritis, which harbours an increased risk for gastric neoplasias, such as intestinal-type adenocarcinoma and Type 1 gastric carcinoids, in particular when extensive intestinal metaplasia (IM) is present.

Data on the prevalence of AG derives from two methodologically different approaches, mainly performed in the general population: serological studies using surrogate markers of gastric function (pepsinogen I, or pepsinogen I/pepsinogen II ratio) or studies using gastroscopy or histology the gold standard for diagnosis of AG. Serological studies reported prevalence rates between 3% and 9%.[2-7] In the population-based Kalixanda study[6] performed in 2008, 6.6% of subjects had AG according to the serological biomarkers (pepsinogen I, II, and gastrin-17). Higher prevalence rates were found in Asian countries: ≤63% was reported by Zou et al.;[7] this may be explained by the inclusion of not only atrophic gastritis with involvement of the body mucosa but also atrophic gastritis

limited to the antrum. However, a recent Swedish serological study[8] showed that AG prevalence among adults aged 35–44 years increased nearly three-fold between 1990 and 2009, but decreased by more than half in participants aged between 55 and 64 years in the same period. This unexpected trend needs to be interpreted within the limits of a serological study using a surrogate marker of AG such as pepsinogen, but the decrease of AG prevalence amongst the elderly might be explained by the stabilising seroprevalence of *H. pylori*. Additionally, the increase in AG stimulated by a high BMI and obesity, as an unexpected positive association between BMI and AG, was also observed. However, it remains to be established whether these novel trends of AG, considered a precursor condition of gastric cancer (GC), may ultimately affect the incidence of GC.

With regard to AG incidence, data are poor and conflicting. A systematic review published in 2010 evaluated the AG incidence in patients free of AG at the time of inclusion in the study.[9] Based on 14 articles, the yearly incidence rates showed a wide range from 0.0–10.9%, probably explained by the very different clinical settings in which the AG diagnoses were made. In a meta-analysis, the ratios comparing the AG incidence in *H. pylori* positive patients to that in *H. pylori* negative patients ranged from 2.4–7.6 with a summary estimate of 5 (95% confidence interval: 3.1–8.3);[9] thus, suggesting a strong relationship between incidence of AG and *H. pylori* infection.

In AG patients, positivity to parietal cells (PCA) and/or intrinsic factor autoantibodies and presence of autoimmune diseases (thyroid autoimmune disease or Type 1 diabetes mellitus) are observed.[10,11] Among 319 AG patients, 53% had an associated thyroid disorder; 76% of these cases were of autoimmune origin.[11] Risk factors for autoimmune thyroid disease in AG patients were female sex (odds ratio [OR]: 5.6), PCA (OR: 2.5), and metaplastic atrophy (OR: 2.2). Thus, autoimmune thyroid disease and AG seem to occur in a closely linked fashion, and this link, formerly described as thyrogastric syndrome, has been included in the autoimmune polyendocrine syndrome IIIb.[12] The thyroid gland and the stomach share some similar morphological and functional characteristics, likely due to their common embryologic origin.[12] AG patients should therefore be screened for occult autoimmune thyroid disease, in particular women and those with positive PCA.[11]

A frequent clinical presentation of AG is pernicious anaemia (PA), a megaloblastic anaemia arising from vitamin B12 malabsorption as a consequence of intrinsic factor deficiency.[13] Another often forgotten presentation of AG may be an otherwise unexplained iron deficiency anaemia, due to iron malabsorption as a consequence of reduced gastric acid secretion together with normal or low vitamin B12 levels.[14] It has been reported that, over time, some of these patients may develop overt PA.[15] The reasons for these different clinical presentations of AG patients having similar gastric histological changes are not fully understood and may have a genetic basis. A panel of single nucleotide polymorphisms related to vitamin B12 absorption investigated in AG patients with and without PA compared to healthy controls showed that a genetic variant of transcobalamin II, related to lower vitamin B12 levels, was more frequently associated in PA patients compared to controls.[16] These data make plausible the idea that genetic factors contribute to determine the clinical manifestation of AG.

From a pathogenetic point of view, AG may arise as a consequence of long-standing *H. pylori* infection or in the context of autoimmune gastritis.[1,9,13] PA, often denoted as a possible advanced stage of AG, is considered an autoimmune disorder.[13] To date, no universally accepted criteria are available to define autoimmune gastritis and to definitively distinguish this clinical entity from chronic, *H. pylori*-driven, multifocal atrophic gastritis. Features that, theoretically, should help to differentiate between autoimmune and non-autoimmune gastritis, such as positivity to intrinsic factor and PCA, presence of enterochromaffin-like cells, PA, and absence of active *H. pylori* infection were observed to be present in similar proportions in patients with body-restricted atrophic gastritis (the classical histological feature of autoimmune gastritis) and those with antral and body atrophic gastritis (more commonly attributed to *H. pylori* infection);[11,14,16-18] thus, the specific features associated with autoimmune gastritis are far from being well defined. AG is a complex condition, consisting of at least three groups: classical autoimmune *H. pylori*-negative AG with spared antrum, multifocal AG involving the antral mucosa with active *H. pylori* infection and often negative for PCA, and a third group with overlapping features (body atrophy with a normal or inflamed antrum, active or past *H. pylori* infection, and PCA positivity).[14,16-19]

The clinical suspicion of AG less frequently arises from specific gastrointestinal symptoms. Traditionally, the clinical spectrum of AG has been considered silent, even if the occurrence of symptoms in this population has been reported. A recent report showed that 56.7% of AG patients presented one or more gastrointestinal symptoms. The vast majority of patients complained of only upper gastrointestinal symptoms, and about a sixth presented lower or both upper and lower symptoms.[20] Dyspepsia, subtype postprandial distress syndrome, was the most represented symptom, present in 60.2% of symptomatic patients. A smaller part of symptomatic patients complained of gastro-oesophageal reflux disease (GORD) (7.2%) and GORD with dyspepsia (17.7%). Logistic regression analysis showed that age <55 years (OR: 1.6), absence of smoking habit (OR: 2.2), and absence of anaemia (OR: 3.1) were independent factors associated to dyspepsia in AG patients. This may be relevant, as guidelines recommend gastroscopy with biopsies for dyspeptic patients >55 years of age or with alarming symptoms;[21] younger dyspeptic patients without anaemia generally are not referred to gastroscopy, thus, possibly missing the diagnosis of AG. In this cohort of AG patients, the prevalence of dyspepsia was roughly two-times higher than that expected in the general population, suggesting a potential role of this condition in the arising of dyspepsia. Delayed gastric emptying has been described in patients with AG.[22] A former study reported in autoimmune gastritis patients the presence of postprandial fullness, early satiety, and epigastric pain in 7.1%, 10.1%, and 35.3%, respectively; a subset of patients complained of heartburn (24.2%) and acid regurgitation (12.1%).[23] Even if in AG patients the most commonly reported symptom was dyspepsia and more recently the attention has been focussed on oesophageal symptoms.

A recent paper investigated the presence of GORD with pH-impedance monitoring in a cohort of autoimmune gastritis patients;[24] 24% of patients were found to be GORD-positive at pH-impedance monitoring, confirming the co-presence of this condition in autoimmune gastritis. Acid gastro-oesophageal reflux rarely occurred whereas non-acid gastro-oesophageal reflux was more frequent, both being involved in the clinical presentation of some patients. Recently, a case was published presenting the unusual co-presence of two conditions, autoimmune gastritis with PA and Barrett's oesophagus, contrasting with the commonly held belief that these two conditions are mutually exclusive.[25] In this hypochlorhydric patient, who complained of dyspeptic symptoms, nausea, vomiting, and thoracic pain; the report also documented conditions typically associated with GORD, ranging from mild erosive oesophagitis to Barrett's oesophagus, during a follow-up of 6 years, showing that gastric acid is not the sole culprit of oesophageal damage. Patients with Barrett's oesophagus have been shown to be have significantly more oesophageal exposure to bile acids and higher oesophageal luminal concentrations of bile acids than GORD patients without Barrett's oesophagus. Some bile salts, as deoxycholic acid, possibly deconjugated by bacteria present in the hypochlorhydric stomach, may cause DNA damage and NF-κB activation in Barrett's cells, a combination that might predispose a patient to cancer development.[26] Thus, in contrast with the classical perception of a mainly silent condition, AG patients may complain of a spectrum of gastrointestinal symptoms, ranging from dyspeptic symptoms to gastro-oesophageal reflux symptoms. Further studies are needed to identify a specific symptomatic pattern in this condition.

DIAGNOSIS OF ATROPHIC BODY GASTRITIS AND PREMALIGNANT CHANGES

AG should be clinically suspected in anaemia, dyspepsia, and in the presence of autoimmune disease, in particular autoimmune thyroid disease, but also in patients with *H. pylori* infection, first-degree relatives of patients with GC or Type 1 gastric carcinoids, and patients chronically using proton pump inhibitors (PPI). Figure 1 shows the clinical scenarios possibly associated with AG.

The worsening of AG by long-term PPI administration was first described in *H. pylori*-positive Mongolian gerbils,[27] and later on this negative relationship was confirmed in humans.[28] The use of PPI in AG patients should be avoided for two reasons: firstly, because PPI treatment may be harmful with regard to the progression of gastric mucosal changes and increase the risk of GC as well as Type 1 gastric carcinoids; secondly, PPI-based treatment is virtually useless in this condition because gastric acid secretion is reduced due to atrophy of parietal cells; as a consequence, the target of the drug, the parietal cell H+/K+ proton pump, is lacking.

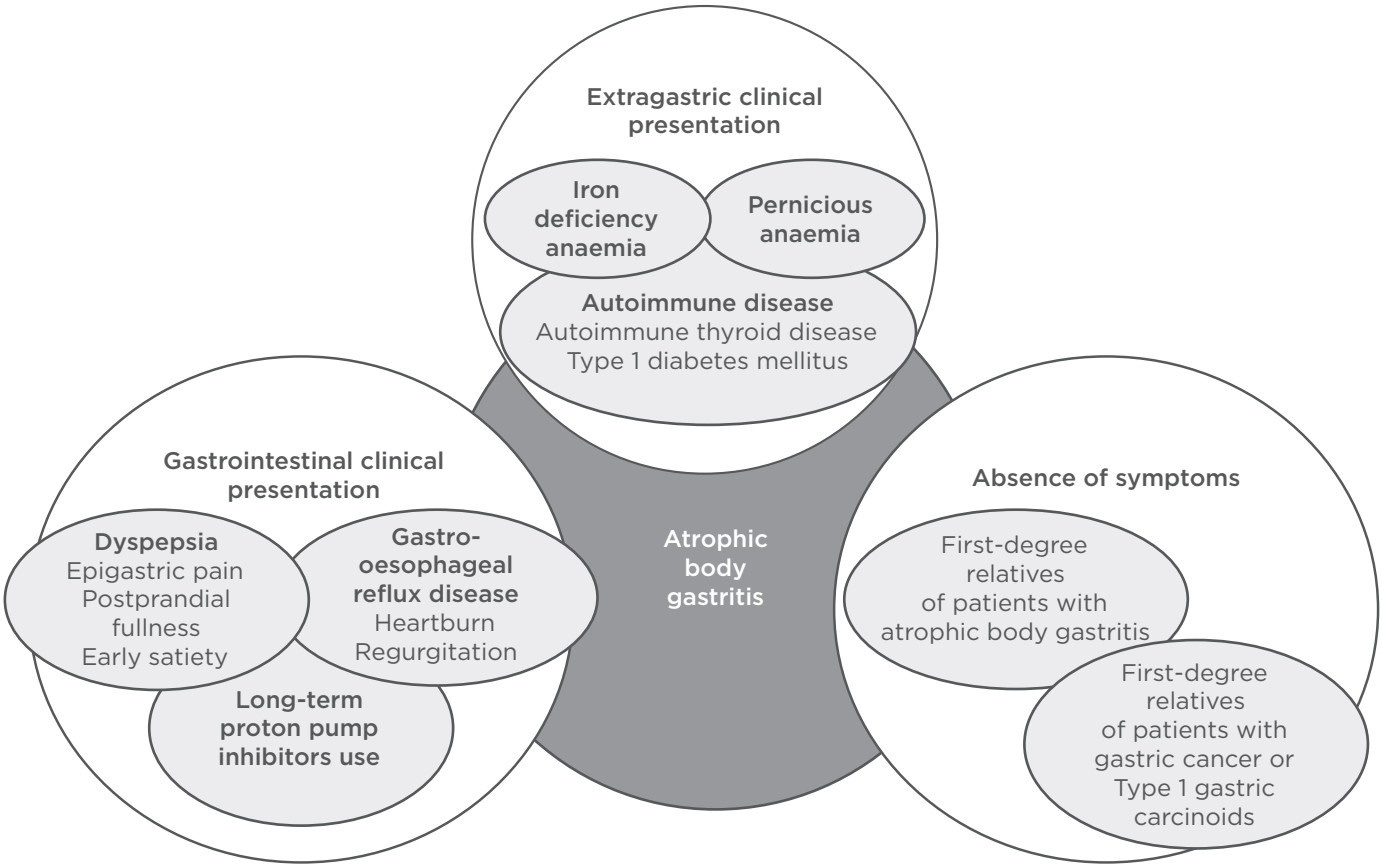

Figure 1: Possible clinical scenario of atrophic body gastritis.

The timely diagnosis of AG is clinically important. The potential micronutrient deficiencies, for example malabsorption of iron and vitamin B12, associated with AG may lead to serious clinical consequences, such as severe chronic anaemia. This may be particularly relevant in the elderly with cardiac comorbidities, in whom a chronic slow decrease of haemoglobin may be noted, with delay leading to life-threatening complications. Vitamin B12 deficiency is a common cause of several neurological and neuropsychiatric disorders, including cognitive impairment, dementia, depression, and myelopathy with or without an associated neuropathy. Vitamin B12 deficiency has been associated with neurologic, cognitive, psychotic, and mood symptoms, and it should be accurately diagnosed and treated early to prevent irreversible structural brain damage and reduce morbidity among elderly patients.[29,30] Iron deficiency has also been recognised as having a negative impact on cognition, behaviour, and motor skills.[31] Considering that in AG both iron and vitamin B12 deficiencies may coexist, a timely and correct diagnosis of this condition is particularly important in the elderly.

AG increases the risk for GC and Type 1 gastric carcinoids. Although the GC incidence has declined over the past decades, especially in Western countries, the mortality rate due to GC remains high.[32] Detection and surveillance of patients with premalignant conditions, including AG and IM, could lead to detection of lesions at an early stage.[33] In Western countries, the gold standard for AG diagnosis is the histopathological evaluation of gastric biopsies, which should include at least five biopsy specimens from antral and body mucosa.[34] This method may be impractical for routine practice because of the time, efforts, and costs required to obtain biopsies and pathology results. The recent position statement from the British Society of Gastroenterology (BSG) on quality standards in upper gastrointestinal endoscopy confirms the need to obtain two non-targeted biopsies from the antrum and body, and one from the incisura, as separate samples. This is carried out in addition to targeted biopsies of any visible lesions, where endoscopic features suggest potential gastric atrophy or metaplasia, in order to confirm this diagnosis and to exclude dysplasia, albeit the grade of evidence is weak.[35] In Japan, gastric mucosal atrophy is commonly diagnosed by endoscopic

appearance, with endoscopic findings of atrophic mucosa consistent with histological findings of atrophic gastritis.[36]

Magnifying narrow-band imaging (M-NBI) has been reported to be useful to predict the presence and distribution of IM in the gastric body. Narrow band imaging is an electronic chromoendoscopy permitting an enhanced visualisation of microvascular architecture and microsurface structure. Several studies reported a good correlation between narrow band imaging appearances and pathology in IM and GC.[37] In M-NBI of the stomach, a light-blue crest is widely known to be a useful endoscopic marker of IM, and, more recently another marker, a white opaque substance without a light-blue crest, has been observed.[38] This innovative endoscopic technique presents a high diagnostic value for gastric precancerous lesions with a high specificity, thus possibly permitting targeting biopsies to optimise diagnostic yield with respect to random biopsies protocols.[39] The above-cited BSG position statement recommends a careful examination of the stomach with white light endoscopy to be performed as a minimum, with evaluation with chromoendoscopy considered.[35]

With regard to the pathological diagnosis of AG, several classifications have been proposed for AG and preneoplastic changes. The updated Sydney System is more frequently used, which combines topographic, morphological, and aetiological information to standardise histological reporting.[34] More recently, operative links for gastritis and IM assessment have been proposed for the staging of gastritis and IM.[40] Unfortunately, classifications are often difficult to use in clinical practice. An Italian survey showed that in routine practice only one third of histology reports were created adhering to the Sydney System, showing that guidelines are poorly observed in clinical practice, possibly representing a critical element for GC surveillance strategies.[41] The full adherence to the Sydney System significantly increased the probability of detecting gastric IM (OR: 9.6) and atrophy (OR: 1.9),[41] thus underlining its potential benefits.

A non-endoscopical diagnostic approach for AG diagnosis is represented by the serological gastric biopsy, including serum pepsinogen I and II and gastrin as well as *H. pylori* antibodies. The diagnostic potential of the serum markers in predicting the mtopography and severity of gastric mucosal disorders has been established.[42,43] According to a meta-analysis, a panel of serological markers (gastrin 17, pepsinogen I and II, and *H. pylori* antibodies) showed a 70.2% pooled sensitivity and a 93.9% pooled specificity in non-invasive diagnosis of AG.[44]

PCA may be considered serological markers of AG, whose potential role in the non-invasive screening or diagnosis is underestimated. PCA are immunoglobulin G against the parietal cell H+/K+ ATPase, are mainly considered serological markers of autoimmune gastritis, and are used to screen patients with other autoimmune disorders for this condition.[14,19] PCA, in particular against the ATP4A and ATP4B subunits of the gastric proton pump H+/K+ ATPase, have recently been shown to be virtually always present in patients with a known diagnosis of AG, by using an innovative luminescent immunoprecipitation system (100% sensitivity for the ATP4A and 95% sensitivity for the ATP4B subunits), and thus represent reliable markers of oxyntic mucosa atrophy.[45] The assessment of immunoglobulin G autoantibodies against ATP4A and/or ATP4B subunits may be proposed as a biomarker not only for autoimmune gastritis, but also for other forms of AG, and positive patients should be advised to undergo gastroscopy with biopsies in order to establish AG diagnosis and to rule out neoplastic complications of this condition.

OUTCOME OF ATROPHIC BODY GASTRITIS: A PRECANCEROUS CONDITION

Gastric mucosal atrophy and IM are known to confer a high risk of GC, thus representing precancerous conditions. The development of the intestinal-type gastric adenocarcinoma represents the end step of an inflammation–metaplasia–dysplasia–carcinoma sequence, called Correa's cascade.[46,47] The intragastric distribution of premalignant changes of the gastric mucosa is one determinant of the GC risk: cases of oxyntic gland atrophy and/or IM distributed in a multifocal pattern, including the lesser curvature of the corpus and fundus, are called multifocal atrophic gastritis, and this phenotype, described as extensive, has been associated with a higher risk of GC. The concept of gastritis of the carcinoma phenotype proposes that the corpus-predominant gastritis increases the risk of GC, likely due to changes in the intragastric milieu (increased pH, reduced ascorbic acid, and scavenging of nitrites).[48,49]

Gastric dysplasia constitutes the penultimate stage of the gastric carcinogenesis sequence and is to be considered a direct neoplastic precancerous lesion. The Padova and Vienna classifications are tools to standardise the terminology for the morphological spectrum of gastric dysplastic lesions. The World Health Organization (WHO) classification[50] provides the diagnostic categories: 1) negative, 2) indefinite, 3) low grade, 4) high grade intraepithelial neoplasia/dysplasia, and 5) intramucosal invasive neoplasia or intramucosal carcinoma.

AG is also associated with Type 1 gastric carcinoids, which are gastrin-dependent, well-differentiated tumours with a generally benign behaviour, representing up to 80% of all gastric carcinoids.[51] Hypergastrinaemia due to AG is the main pathogenetic factor for Type 1 gastric carcinoids acting as a growth factor for enterochromaffin-like cells; through a multistep process passing from hyperplasia to dysplasia, carcinoids may develop.[51]

Many efforts have been made to quantify the risk of gastric neoplasms in AG patients. A varying progression rate of AG to GC, up to 2% per year, has been reported at follow-up periods of up to 16 years.[52,53] A systematic review showed in AG patients with PA an estimated seven-fold relative risk of GC.[54] Data on long-term incidence of Type 1 gastric carcinoids are scarce; a cohort study reported an annual incidence rate for Type 1 gastric carcinoid of 0.4%.[53]

In AG patients, the cost-effectiveness of regular endoscopic follow-up for GC surveillance is not established. The Management of precancerous conditions and lesions in the stomach (MAPS) guidelines recommend a surveillance for GC for patients with extensive atrophic gastritis or IM,[55] but these guidelines are not addressed to PA patients because PA is not considered to be part of the precancerous cascade.[46] According to the above-reported studies,[53,54] a different clinical management of AG patients with or without PA does not seem justified. A cost analysis by surveillance endoscopy in AG in Italy showed that at the 361 surveillance gastroscopies, 20 neoplasias were detected, corresponding to a number-needed-to-screen of 19 and a cost-per-gastric-neoplastic-lesion of €2,945. By restricting surveillance to PA patients, the number-needed-to-screen and the cost-per-neoplasia was reduced to 13.8 and €2,139, respectively, and still detected 74.0% of neoplasias, thus confirming the association of PA with GC and supporting the need of surveillance in this condition. PA may be viewed as one of the risk factors allowing an efficient allocation of endoscopic surveillancein AG in a low-risk country.[56]

With regard to the combined risk of GC and carcinoids, a recent study[57] assessed the occurrence of GC and carcinoids in a cohort of AG patients at long-term follow-up from 4 years onwards. The annual incidence rates per person-year were 0.25%, 0.43%, and 0.68% for GC, dysplasia, and Type 1 gastric carcinoids, respectively; the incidence rates of GC and Type 1 gastric carcinoid were the same (p=0.07), indicating that AG patients are similarly exposed to both risks.

The occurrence of GC in patients with Type 1 gastric carcinoids was described in 23.0% (4 of 17) patients with Type 1 gastric carcinoids in a median follow-up period of 6 years.[57] Three cases were intestinal-type adenocarcinomas and one was signet ring cells diffuse GC, localised in three cases in the antrum. Thus, the surveillance of Type 1 gastric carcinoids patients with an accurate bioptic sampling of antral mucosa seems of benefit. Long-standing hypergastrinaemia may explain why patients with Type 1 gastric carcinoids might develop more frequently GC. Hypergastrinaemia has been proposed in many models of gastric carcinogenesis and seems to be a common causative factor in otherwise different circumstances.[58] Also, the long-term conservative management of Type 1 gastric carcinoids exposes these patients to a higher risk of GC.

CONCLUSION

AG is an underdiagnosed and mainly benign condition, which may clinically present with upper gastrointestinal symptoms, but also with extragastrointestinal signs or symptoms. This condition may harbour two underhand consequences; firstly, the increased risk for two types of gastric neoplasms, GC and Type 1 gastric carcinoids; secondly, the occurrence of erythropoietic micronutrient deficiencies potentially leading to anaemia due to iron or vitamin B12 deficiency which need prompt treatment. Patients with clinical suspicion of AG should undergo serological screening by serum pepsinogen I and II, gastrin, and/or *H. pylori* antibodies, in order to better address gastroscopy. Another useful screening tool of AG is represented by PCA assessment. The definite diagnosis still delays on gastroscopy and pathological evaluation of multiple body and antral biopsies, possibly

staged by the updated Sydney System, operative link for gastritis, and IM assessment. Innovative endoscopy techniques, such as M-NBI, may in a near future allow to target biopsies at surveillance endoscopy improving the early detection of gastric neoplasms.

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ARE WE READY FOR BIOSIMILARS IN GASTROENTEROLOGY?

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ABSTRACT

Biologics are large complex molecules that are produced in living systems. They have revolutionised the treatment of patients suffering from various diseases, including inflammatory bowel disease. However, in many parts of the world, patient access to biologics has been hampered, mainly because of the high costs associated with these therapies. Since the patent expiration of several of these biologics, biosimilars have emerged, promising equal effectiveness and safety for patients but at a more affordable price. Despite this, concerns remain regarding the use of biosimilars as replacements for biologics. This review discusses the issues and controversies surrounding the development and applicability of biosimilars in the field of gastroenterology.

Keywords: Biologics, biosimilar, Crohn's disease (CD), extrapolation, inflammatory bowel disease (IBD), ulcerative colitis (UC).

INTRODUCTION

Biotherapeutic agents, also known as biologics, are large complex molecules that are produced in living systems.[1] Biologics comprise a range of molecules with varying complexities, including peptides, such as human insulin; small proteins, like erythropoietin; and large molecules, including monoclonal antibodies.[2] The use of biologics in the field of gastroenterology is largely confined to the treatment of the immune-mediated inflammatory bowel diseases (IBD), such as ulcerative colitis (UC) and Crohn's disease (CD). There are four biological agents that target tumour necrosis factor (TNF)-α (anti-TNF-α therapies); namely, infliximab, adalimumab, certolizumab pegol, and golimumab. Additionally, there are two cell adhesion molecules approved for use in IBD that target α4-integrin and α4β7-integrin, known as natalizumab and vedolizumab, respectively. The use of biologics has revolutionised the treatment of IBD by significantly improving outcomes while maintaining a good safety profile.[3]

However, one important limiting factor for the use of biologics in clinical practice is the considerably high cost of this treatment. This factor, coupled with the actual or impending patent expiration of biologics, has given rise to the development of highly similar copy versions of the originator or reference drug, known as biosimilars. The World Health Organization (WHO) defines a biosimilar as a biotherapeutic product that is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product.[4] The infliximab biosimilar CT-P13, marketed under the trade name of Remsima™ or Inflectra®, was the first biosimilar licensed for use in IBD treatment in Europe, receiving approval from the European Medicines Agency (EMA) in 2013.[5] This was followed by Flixabi®, which received approval in 2016.[6]

MANUFACTURING PROCESS

Although biosimilars are only marketed after expiration of the reference drug's patent, much like small-molecule generic drugs, they are not considered to be generic drugs. This is due to

several key differences between biologics, biosimilars, and small-molecule drugs; biologics differ significantly from small-molecule drugs in their size, complexity, and manufacturing process. In addition, while small-molecule drugs typically have a molecular weight of between 0.1 and 1.0 kDa, biologics have much larger and more complex chemical structures, commonly ranging from 18–150 kDa.[7] Small molecule drugs are produced by chemical synthesis, while biologics are typically produced by living cells through complex manufacturing and purification processes. They also differ in their route of administration; small molecule drugs are generally administered orally, while biologics are most often delivered via the parenteral route. Biologics also have greater immunogenic potential, in part due to their larger size, compared to small-molecule drugs, which are generally non-immunogenic.[7,8] Infliximab is known to carry more clinical consequences due to immunogenicity compared to etanercept and filgrastim, including loss of response and infusion reactions.[9]

Biosimilars are unlikely to be the exact replica of the originator drug because of the complex manufacturing process and lack of access to the original cell line. Typically, the manufacturing process of biologics requires multiple steps for cloning, selecting, maintaining, and expanding the cell line; and isolating, purifying, and characterising the product. However, this is not the case for small-molecule generic drugs, where it is possible to generate an identical molecule through a series of predictable chemical reactions. Developers of biosimilars usually do not have access to the manufacturing details of the reference drug and therefore need to develop their own manufacturing process capable of producing a product closely resembling the originator product. Manufacturing differences between a biosimilar and the reference drug can lead to differences in molecular structure, content, biological activity, and immunogenicity. However, any given biological product is likely to be modified several times throughout its life cycle, after which it is unlikely to resemble its original version at marketing authorisation.[10]

REGULATORY LANDSCAPE

To establish that the proposed biosimilar meets the requirements for biosimilarity, regulatory agencies require a rigorous, stepwise biosimilarity assessment. There are several regulatory pathways for the development of biosimilars worldwide, notably by the EMA, the U.S. Department of Health and Human Services (HHS), and the U.S. Food and Drug Administration (FDA). Although there is a slight difference in the regulatory requirements, the basic principles governing both pathways are very similar.[7]

The European Union (EU) pioneered the development of regulatory requirements for biosimilars in 2005 when the EMA published a general framework guideline to introduce the principles of biosimilarity. The EMA was also the first regulatory agency to give marketing authorisation for biosimilars in 2006. The outline of the regulatory approach includes comparing the proposed biosimilar with its reference product in analytical and clinical studies to demonstrate similarity with regard to quality, safety, and efficacy.[11]

In practice, regulatory authorities require two phases of clinical trials for approval of a biosimilar product for one indication, including a Phase I study to demonstrate equivalence in terms of pharmacokinetics, pharmacodynamics, and safety. An adequately powered, randomised, parallel group Phase III clinical study is subsequently carried out to demonstrate no clinically meaningful difference with respect to efficacy, safety, and immunogenicity between the biosimilar and the reference product.[3]

EXTRAPOLATION

Extrapolation refers to the idea that clinical studies of biosimilars can be performed in one disease state or population group and then inferred to work in other disease settings or indications for which the reference biologic is approved and licensed. In the EU, in cases where the effectiveness of biosimilarity has been recognised in one indication, extrapolation to other disease settings of the reference product may be acceptable, providing appropriate scientific justification is provided.[12] Similarly, in the USA, guidelines state: "sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought."[13] To support extrapolation, a biosimilar needs to demonstrate similarity of mechanism of action, target-binding characteristics, pharmacokinetics, and biodistribution to the originator drug in clinical tests and the extrapolated indications. Furthermore, any expected differences in toxicity or effectiveness must be addressed.

CT-P13 is an infliximab biosimilar that has received marketing authorisation for all indications of infliximab through extrapolation of efficacy and safety data. In a series of analyses, CT-P13 was shown to have identical primary and higher order structures to infliximab; monomer and aggregate contents, overall glycan types, and distribution were indistinguishable, and potencies and binding affinities were comparable to infliximab.[14]

In a Phase I, randomised, double-blind study (PLANETAS),[15,16] the pharmacokinetics, safety, and efficacy of CT-P13 was compared to its originator infliximab, Remicade®, in patients with ankylosing spondylitis. The equivalent pharmacokinetics profile and comparable tolerability, safety, and efficacy, prompted Celltrion (Incheon, South Korea) to undertake a Phase III, randomised double-blind study (PLANETRA)[17,18] to demonstrate equivalence in the efficacy and safety of biosimilar infliximab CT-P13 compared with the originator infliximab, Remicade, when co-administered with methotrexate in patients with active rheumatoid arthritis. There were no significant differences in the efficacy, safety, or pharmacokinetic profile between biosimilar infliximab CT-P13 and Remicade. Similar immunogenicity was also observed in patients with rheumatoid arthritis or ankylosing spondylitis who switched from Remicade to CT-P13.[19,20]

Following these studies, CT-P13 received regulatory approval in South Korea in July 2012[21] and subsequently became the first biosimilar to infliximab to receive regulatory approval by the EMA (in September 2013)[22] and by the FDA (in April 2016)[23] for all the therapeutic indications for which infliximab was previously authorised (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, adult CD, paediatric CD, adult UC, and paediatric UC).

In 2016, SB2 (marketed as Flixabi) became the second infliximab biosimilar to obtain regulatory approval in Europe for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, adult CD, paediatric CD, adult UC, and paediatric UC.[6] The approval of SB2 was based on data derived from a randomised Phase I pharmacokinetic study comparing SB2 and Remicade in 159 individuals,[24] and a randomised, double-blind, multinational, parallel-group, Phase III study comparing SB2 to the infliximab reference product in 584 patients with moderate-to-severe rheumatoid arthritis who were already receiving methotrexate therapy.[25]

The concept of extrapolation is not free of issues. Health Canada previously did not approve the extrapolation of indications to CD, UC, or paediatric patients due to the differences in the levels of fucosylation, FcγRIIIa binding, and some *in vitro* trials for antibody-dependent cell-mediated cytotoxicity. However, despite the lower *in vitro* antibody-dependent cell-mediated cytotoxicity activity of CT-P13, these differences disappeared under physiologic conditions, questioning the clinical relevance of the observed differences in FcγRIIIa binding.[26] Furthermore, the binding of the test and reference product to the soluble and/or membrane-bound TNF-α were comparable. Inhibition of TNF on epithelial cells and induction of regulatory macrophages were also similar.[10]

BIOSIMILARS IN INFLAMMATORY BOWEL DISEASE

Several studies have shown CT-P13 to be effective and well-tolerated in patients with CD or UC,[27-38] including two studies involving paediatric patients.[33,34] In addition, it is the only biosimilar to have real-world data on patients with IBD. An observational cohort study conducted in Hungary of 210 patients with IBD (22% of the patients had been previously exposed to infliximab) reported induction data for CT-P13.[27] At Week 14, 81% of patients with CD and 78% of patients with UC showed clinical response; 54% of patients with CD and 59% of patients with UC were in clinical remission. Patients were followed up to Week 30 and adverse events were experienced in 17% of the individuals; infusion reactions and infectious adverse events occurred in 7% and 6% of all patients, respectively. A Norwegian study of 78 patients (46 with CD and 32 with UC)[28] and two Korean studies, the first of which included 173 patients (95 with CD and 78 with UC) and the second of which comprised 110 patients (59 with CD and 51 with UC),[29,30] similarly reported excellent induction results.

A prospective cohort study of 83 patients with IBD conducted by Smits et al.[31] showed that switching from Remicade to CT-P13 did not have a significant impact on short-term clinical outcomes. The NOR-SWITCH trial,[32] a randomised, non-inferiority, double-blind, Phase IV trial with 52 weeks of follow-up, showed that switching from Remicade to CT-P13 was not inferior to continued treatment with Remicade. Similarly, Sieczkowska et al.[33] demonstrated that switching from Remicade to

CT-P13 is an effective and safe option in children with IBD; induction therapy with CT-P13 in children with CD was also shown to be effective.[33]

In a study of 125 patients with IBD and healthy controls, Ben-Horin et al.[39] showed that anti-Remicade antibodies in patients with IBD recognise and functionally inhibit CT-P13 to a similar degree, suggesting similar immunogenicity and shared immunodominant epitopes on these two infliximab agents. Finally, a study by Gils et al.[40] concluded that the assay for therapeutic drug monitoring of Remicade can also be used to determine Remsima and Inflectra concentrations, and that in all patients with IBD who develop anti-Remicade antibodies, the antibodies cross-react with infliximab biosimilars.

In view of these results, the British Society of Gastroenterology (BSG) concluded that there is sufficient data to show that safety, clinical efficacy, and immunogenicity of CT-P13 are similar to the reference biologic, and that switching from infliximab to CT-P13 is safe and effective.[41] This position also reflected that of the European Crohn's Colitis Organisation (ECCO), which stated: "data for the usage of biosimilars in IBD can be extrapolated from other indications" and "switching from the originator to a biosimilar in IBD is acceptable."[42]

IMMUNOGENICITY

Anti-drug antibodies (ADA), typically IgG antibodies with neutralising and binding properties, can lead to reduced efficacy and a reduction in anti-TNF levels and allergic reactions. ADA have been documented in up to 60% of patients with CD when infliximab was used on an ad hoc basis and 10–20% of patients in randomised controlled trials of maintenance therapy.[43,44] The PLANETAS and PLANETRA studies showed no difference between ADA formation in subjects treated with originator infliximab or CT-P13 at Weeks 52[15,17] and 104.[19,20] As mentioned previously, the study by Ben-Horin et al.[39] showed high similarity in binding, resulting in similar immunogenicity and the presence of shared immune-dominant epitopes between CT-P13 and the reference product infliximab. The NOR-SWITCH study[32] also established no differences in ADA formation between patients who switched to CT-P13 and all the study patients.

With regard to SB2, 55.2% in the SB2 treatment group developed ADA compared to 49.7% in the infliximab group; however, this was not statistically significant. Trough levels of infliximab were similar between SB2 and infliximab over time and were also similar in each ADA subgroup (ADA-positive and ADA-negative) between SB2 and infliximab.[25]

INTERCHANGEABILITY AND SUBSTITUTION

Interchangeable means that the biological medicinal products can be substituted for one another, without loss of efficacy or decrease in safety. To be considered interchangeable, the efficacy and safety risk of a biosimilar should not be greater than that of the reference biologic.[45] Substitution is the practice whereby a branded product can be swapped and occurs at the dispensing level when a pharmacist elects to change a product without the prescribing physician's prior consent.

According to the FDA: "interchangeable products are both biosimilar to an FDA-approved reference product and can be expected to produce the same clinical result as the reference product in any given patient."[46] If administered more than once to a patient, the risk in terms of safety or efficacy of alternating or switching (between biosimilar and originator) must not be greater than the risk of using the reference product without alternating or switching. An interchangeable product may also be substituted at pharmacy level without the intervention of the prescribing physician.[46]

There are differences in the legislations for interchangeability and substitution between the USA and the EU. The FDA has the authority to designate a biosimilar as interchangeable, but substitution is regulated at state level. Many states in the USA have already developed proposals for the substitution of innovator biologic agents with biosimilars at the pharmacy level. Provision of state legislations vary, but they have several common features and substitution is permitted only if the FDA has designated the biosimilar as interchangeable; however, substitution is prohibited if the prescribing physician has indicated a preference for the reference product and the patient must be notified that a substitution has been made.[46] As of November 2016, 36 states have considered legislation to establish standards for biosimilar substitution and 25 have enacted substitution laws.[47] In comparison, the EMA has abstained from providing guidance on interchangeability, leaving this decision to the respective national authorities.[48] France was the first EU member to

explicitly authorise biosimilar substitution for naïve patients (those who had received neither the innovator drug or the biosimilar).[49] However, switching, interchangeability, and substitution are under discussion in other EU countries.[50-52]

Physicians often have to make the decision about switching from the reference biologic (Remicade) to a biosimilar (Inflectra, Remsima, or Flixabi). In the future, they will need to also consider a switch in the opposite direction (reverse-switch) or from one biosimilar to another (cross-switch) and this explains why detailed rules for interchangeability and substitution are warranted; the design of these rules will also determine the extent to which they will promote or limit substitution in the future.[53]

ECONOMIC CONSIDERATIONS

The main purpose of producing biosimilars is to reduce the costs of drugs. In 2007, $286.5 billion was spent on prescription drugs in the USA, of which $40.3 billion was for biologics. It has been estimated that a biosimilar will cost $100–200 million to develop, according to figures from DiMasi et al.,[54] and an innovator biologic costs ≥$800 million.[54,55] Due to reduced testing requirements for approval, it has been approximated that biosimilars will cost 20–40% less than their reference products.[56]

As a result of biosimilar use, cumulative savings to healthcare systems in the EU and USA could total >$56 billion and might reach as high as $112 billion.[57] Moreover, the reduced costs could also increase patient access to biologic therapies; access to biologic drugs was not possible in 10 out of 46 European countries in 2014, due to cost constraints.[58] Notably, patient access to biologic treatments has grown by as much as 100% following the availability of biosimilars.[57]

Due to the sizeable costs associated with manufacturing, quality control, marketing, storage, and special requirements for pharmacovigilance, the price reduction of biologic agents might not be as profound as for generics of small-molecule medicines (competition between multiple manufacturers ultimately drives prices of generics down by 50–80% in most markets).[59,60] In the EU, where biosimilars have been available for several years, the prices have been lowered by an average of ˜30% compared to those of the reference products.[61,62] However, there is considerable variation in price reductions between European countries,[63] with the most impressive price discount of 69% seen for CT-P13 in Norway.

CONCLUSION

Although biologic therapy has revolutionised the treatment of many inflammatory conditions, including IBD, access to this therapeutic option has been hampered by its high cost. CT-P13 was the first infliximab biosimilar to obtain approval by the EMA in September 2013, followed by Flixabi in 2016. Even more biosimilars are in the development pipeline and data on adalimumab biosimilars have started to become available.[64,65] Extrapolation is a valid, evidence-based process, and state-of-the-art physicochemical and biological characterisation studies show high similarity between CT-P13, Flixabi, and originator infliximab. The introduction and availability of biosimilars has already widened patients' access to such important treatment, and this will lead to a change in the landscape of managing many chronic inflammatory conditions, including IBD. With mounting evidence that shows CT-P13 is effective and well-tolerated among IBD patients, we conclude that the gastroenterology field is ready for biosimilars.

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PAEDIATRIC *HELICOBACTER PYLORI* INFECTION IN TAIWAN: CURRENT STATUS AND PERSPECTIVES

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ABSTRACT

Helicobacter pylori infection is the most prevalent chronic bacterial infection in the world. The prevalence of *H. pylori* infection ranges from approximately 10–90% and is influenced by age, country, socioeconomic status, nutritional status, urbanisation, hygiene, and diagnostic tools available. In general, chronic *H. pylori* infection can lead to chronic antral gastritis, peptic ulcer disease, primary gastric lymphoma, and gastric adenocarcinoma. As public hygiene and sanitation have improved, the rates of *H. pylori* infection and related diseases have been declining annually in developed and rapidly developing countries, although the infection is still common in some geographic areas. In Taiwan, an Asian country with a high incidence rate of gastric malignancy, there is a similar trend of declining *H. pylori* prevalence rates. Prevalence rate differed vastly between rural and urban areas; however, rates have fallen greatly in recent decades. Optimal treatment of *H. pylori* infection in children has not yet been determined and will require further collaborative studies. However, eradication failures are concerning since global rates of antibiotic resistance are increasing and therapy for *H. pylori* infection is increasingly prescribed. In Taiwan, the overall antimicrobial resistant rates to clarithromycin, metronidazole, and levofloxacin were 23.4%, 20.3%, and 11.8%, respectively. With the propagation of public health education, advancement of diagnostic tools, and patient-specific tailoring of therapeutic strategies, the prevalence and eradication failure rate of *H. pylori* infection in children should improve in the near future, both in developed and developing countries.

Keywords: Antibiotic resistance, children, *Helicobacter pylori*, prevalence, Taiwan.

INTRODUCTION

Helicobacter pylori infection is the most prevalent chronic bacterial infection in the world. The prevalence of *H. pylori* infection ranges from approximately 10–90% and is influenced by age, country, socioeconomic status, nutritional status, urbanisation, hygiene, and diagnostic tools available.[1-3] *H. pylori* was discovered by Warren and Marshall in 1983.[4] Infection is generally acquired in early childhood, primarily by mother–child and sibling–sibling transmission, and is usually life-long in the absence of effective treatment.[5,6] Chronic *H. pylori* infection can lead to chronic antral gastritis, peptic ulcer disease, primary gastric lymphoma (most commonly mucosa-associated lymphoid tissue [also known as MALToma]), and gastric adenocarcinoma.[7-9] More recently, it has been suggested that *H. pylori* may be associated with extra-intestinal disorders, including short stature, immune thrombocytopenic purpura, refractory iron deficiency anaemia (IDA), vitamin B12 deficiency, and eye, skin, respiratory, and psychiatric disorders.[4,7,8] However, *H. pylori* infection may be beneficial for several diseases, such as asthma, obesity, and inflammatory bowel disease.[8,10]

Despite worldwide prevalence of chronic *H. pylori* infection, the route of transmission is still unclear. Interpersonal transmission appears to be the main route, although environmental transmission, such as drinking contaminated water, remains possible. Intrafamilial infection rather than community-acquired infection has also been proposed.[5] In our previous study on *H. pylori* infection in children in northern Taiwan, we found no significant association between the patients' blood type, age, sex, source of

water supply, parents' educational level, or the status of family members' *H. pylori* seropositivity.[11] It is therefore essential that we improve our understanding of *H. pylori* infection in children in Taiwan, an Asian country with a high incidence rate of gastric malignancy.

EPIDEMIOLOGY

The prevalence of *H. pylori* infection in children varies between 4.9% and 73.3% worldwide, depending on country, geographic area, target population, patient age, year of specimen collection, sample size, and detection methods used in the studies.[5,12,13] As general public hygiene and sanitation improves, the rates of *H. pylori* infection and related diseases have been declining yearly in developed and rapidly developing countries, although the infection is still common in some geographic areas.[14] According to the 1996 National Health and Nutrition Examination Survey in the USA, 24.8% of participants aged 6–19 years displayed evidence of *H. pylori* infection.[15] However, the rate of infection in the 0–20-year age group decreased to 6.0% in a 2012 study carried out in Texas, USA.[16] In Russia, the seroprevalence of *H. pylori* declined from 30.0% among children aged <5 years in 1995 to 2.0% 10 years later.[17] Studies from Asian countries also have shown decreasing rates of *H. pylori* infection over the past 40–50 years.[18] In Japan, the overall seroprevalence rate decreased from 72.7% in 1974 to 39.3% in 1994, which has led to a decline in the number of cases of gastric cancer in Japan.[19] In a study including children from the Guangzhou province in southern China, the seroprevalence of *H. pylori* was found to significantly decrease from 62.5% in 1993 to 49.3% in 2003.[20] Figure 1 summarises the global prevalence rates of *H. pylori* in children during recent decades.

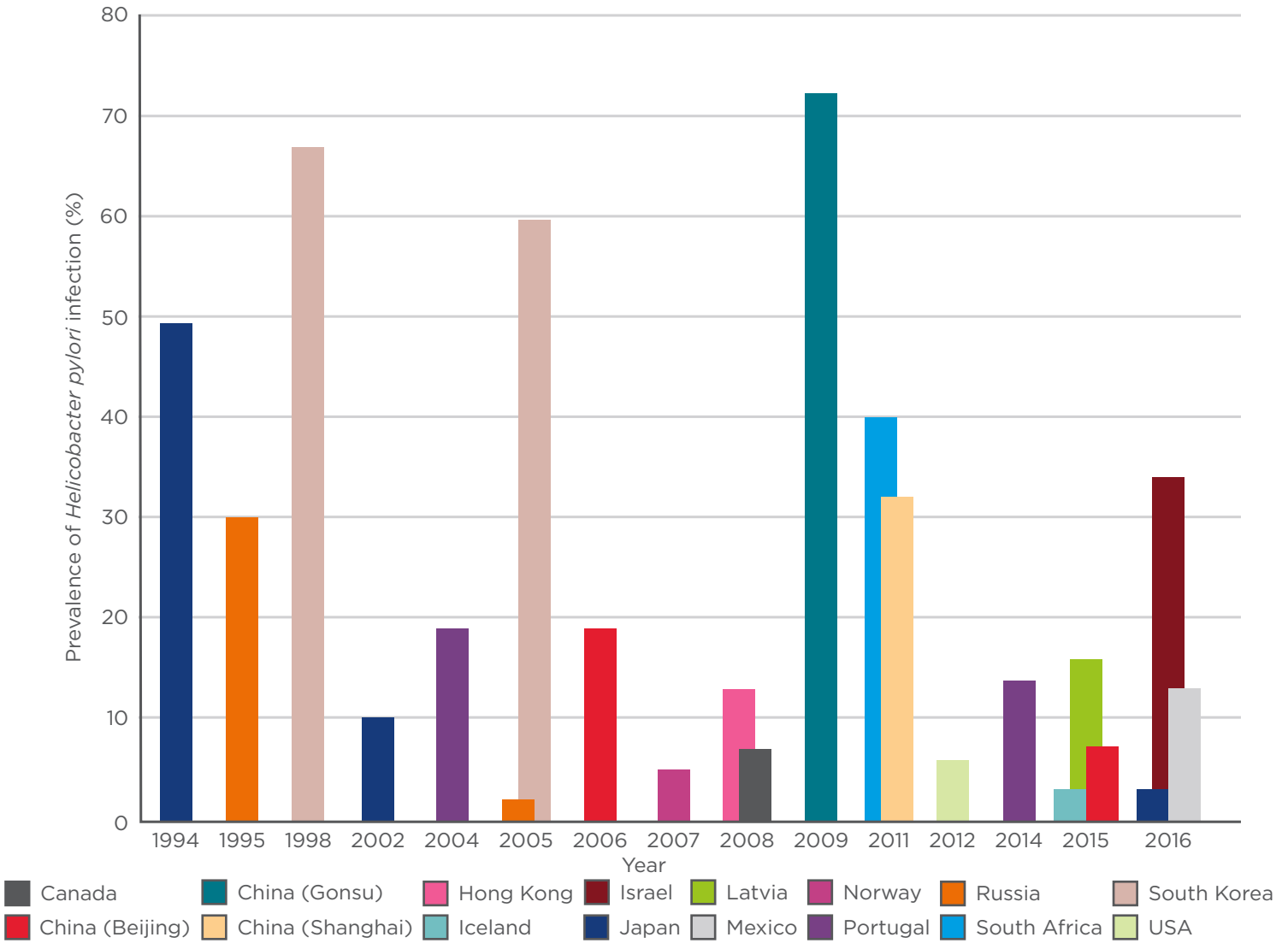

Figure 1: Global prevalence of *Helicobacter pylori* infection in children.

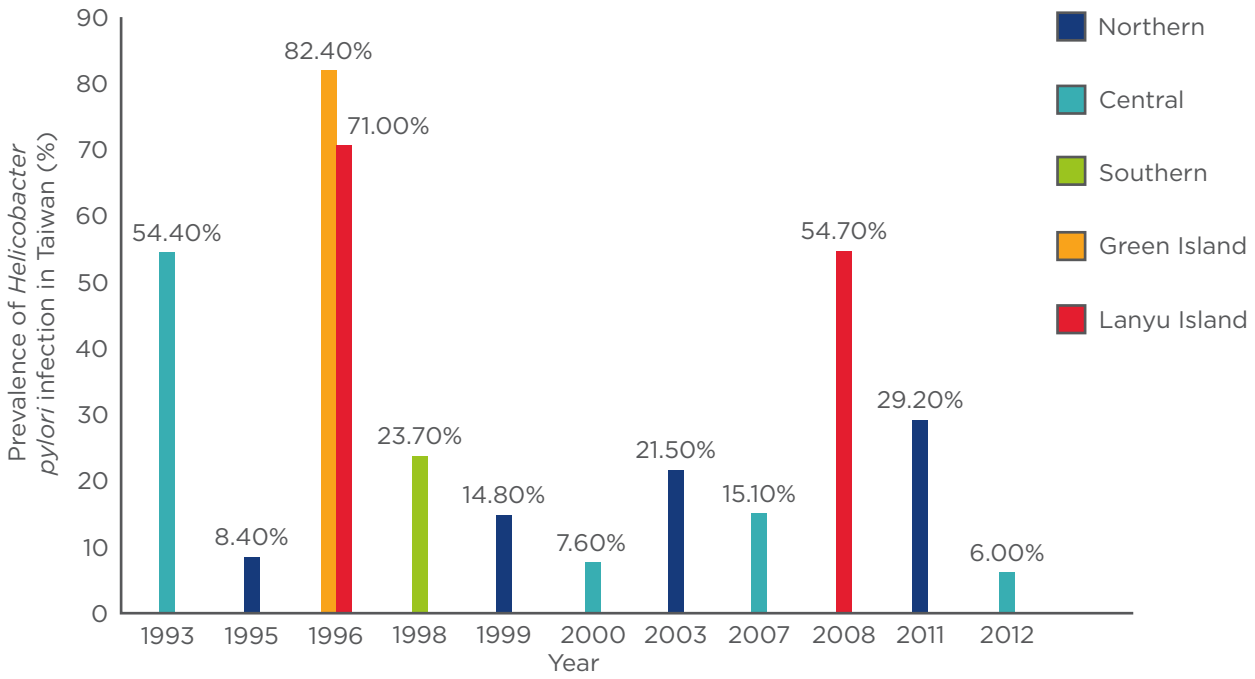

Figure 2: Prevalence of paediatric *Helicobacter pylori* infection in Taiwan.

In Taiwan, several seroprevalence studies were performed in different districts in recent decades. We also found the similar trend of declining prevalence rate; Figure 2 shows the seroprevalence rate in different regions in Taiwan over the last 20 years. The prevalence rate differed greatly between rural and urban areas and has fallen dramatically in recent decades. In a study performed in two rural islands of Taiwan in 2005, Chen et al.[21] reported that the seroprevalence of *H. pylori* among the randomly selected school-aged children (13–15 years) on Green Island and Lanyu Island were 82.4% and 71.0%, respectively (Figure 2). In 2008, Chi et al.[22] also reported that the *H. pylori* infection rate based on carbon-13 urea breath test in Lanyu Island was 54.7% in secondary school students. There was a decline in the prevalence rate in this isolated and closed island following the introduction of public health education regarding proper sanitation and food handling. However, the rate was still high when compared to that of mainland Taiwan.

In a study in rural central Taiwan in 2015, Wu et al.[23] found that the overall *H. pylori* infection rates were 6.0% in children between 0 and 15 years of age, much lower compared to previous studies of the same region. In our previous study in northern urban Taiwan in 2003, the seroprevalence of *H. pylori* in primary school students, aged 7–12 years, was 21.5%, which was higher than that reported in previous Taiwanese reports.[11] Chiu et al.[24] also found that the total prevalence of *H. pylori* infection in children aged 4–18 years was 29.2% in northern urban Taiwan in 2011; however, the age-specific seroprevalence of *H. pylori* infection in Taiwan was 40.9% for the 10–19 year age group in a nationwide study.[25] Age and urbanisation were found to be dependent factors for the variations in prevalence rates found in different studies (Figure 2).

CLINICAL MANIFESTATIONS

Gastritis and Peptic Ulcer Diseases

While infection with *H. pylori* infection is common, the spectrum of the disease is wide and complex; it is associated with many disorders, most strongly with chronic gastritis and peptic ulcers.[26] *H. pylori* infection is also associated with chronic antral gastritis, which is related to duodenal ulcer, gastric ulcer, and gastric carcinoma. Many endoscopic studies have supported the association between *H. pylori* infection and gastroduodenal pathology in children.[27]

A pooled analysis of early reports demonstrated that the rate of antral gastritis for children with *H. pylori* infection (compared with uninfected subjects) ranged from 1.9–71.0%.[28] The prevalence of *H. pylori* in children with duodenal ulcers was high compared with children with gastric ulcers.[28] A subsequent retrospective study from Japan confirmed that the prevalence of *H. pylori* was

very high in antral gastritis and duodenal ulcer patients (98.5% and 83.0%, respectively). In another retrospective review of 619 Chinese children who had undergone upper endoscopy for investigation of upper gastrointestinal symptoms, Tam et al.[29] found that 6.9% had a peptic ulcer; the prevalence of *H. pylori* infection was present in 56.8% of duodenal ulcer and 33.3% of gastric ulcer patients.

In a study from southern Taiwan, Huang et al.[30] reported 47.7% of childhood peptic ulcer disease cases had *H. pylori* infection, and 16.5% of the children reported previous use of non-steroidal anti-inflammatory drugs (NSAID). Children with *H. pylori*-related peptic ulcer disease had a significantly higher mean age, antral chronic inflammatory score, rate of familial peptic ulcer disease, and presence of duodenal ulcer and nodular gastritis than those with NSAID-related and non-*H. pylori*, non-NSAID-related peptic ulcer diseases.

However, there have been conflicting results of studies looking for an association between infection with *H. pylori* and peptic diseases in children. In a prospective European multicentre pilot study on the incidence of gastric and duodenal ulcer disease in children, Kalach et al.[31] found that ulcers occurred in only 10.6% of cases, with *H. pylori* infection reported in only 26.7% of these. In our recent study performed in northern Taiwan, 56.8% of children with *H. pylori* infection were completely asymptomatic, and the remaining 45.2% had at least one gastrointestinal symptom.[24] Our result supported the hypothesis that the abdominal complaints found in children with *H. pylori* infection were not caused by the infection itself.

Recurrent Abdominal Pain

The relationship between recurrent abdominal pain (RAP) in childhood and *H. pylori* infection is still not clear;[28] the results of two uncontrolled trials have suggested improvement of clinical symptoms after *H. pylori* infection eradication.[32,33] In a meta-analysis of 38 studies between 1966 and 2009, Spee et al.[34] found no association between RAP and *H. pylori* infection in children. In a study in Icelandic children, any abdominal pain in the previous 6 months was reported by 36% of *H. pylori*-negative children and 43% of *H. pylori*-positive children.[6] This was a considerably lower prevalence than that reported in other studies, including in a Swedish study where RAP was recorded at 13%, and any abdominal pain was reported by 63% and 70% of children in Sweden[35] and Germany,[36] respectively. Large-scale multicentre trials performed in children are required to uncover whether a connection exists between *H. pylori* infection and RAP.

Gastro-oesophageal Reflux Disease

Recently Daugule et al.[37] showed a significantly higher prevalence of *H. pylori* among patients with reflux oesophagitis compared to patients with hyperaemic gastropathy alone. The prevalence of reflux oesophagitis was 14.2% among *H. pylori*-positive and 3.3% among *H. pylori*-negative patients with an odds ratio of 5.5 for *H. pylori* infection among children with reflux oesophagitis. However, *H. pylori* has been found to be inversely correlated with the prevalence of gastro-oesophageal reflux disease, and certain studies have shown aggravation of oesophagitis after eradication.[7] A Hong Kong study found that *H. pylori* eradication was the only predictor of gastro-oesophageal treatment failure.[38] They also showed *H. pylori* eradication increased oesophageal acid exposure and might adversely affect the clinical course of reflux disease in a subset of patients.[39]

Iron Deficiency Anaemia

Over the past two decades, an association between *H. pylori* and paediatric IDA has been established.[8] However, the issues of whether paediatric *H. pylori* infection is linked causally to IDA and whether treatment or resolution of *H. pylori* infection would improve iron stores in children are still matters of great debate. It is often difficult to distinguish between the confounding effects of poverty, poor nutrition, and poor compliance with treatment when examining the relationship between *H. pylori* and anaemia. While studies have shown that eradication of *H. pylori* in children with refractory anaemia results in improved haematologic indices in the short term, no study, until now, had sufficient follow-up time to determine if there is a recurrence of anaemia after treatment.

One explanation for the relationship between *H. pylori* infection and IDA involves the effect of *H. pylori* gastritis on gastric acid secretion and iron absorption.[8] Non-haem iron accounts for 80% of dietary iron in industrialised countries,[40] and hydrochloric acid in acid secretions is crucial to the effective absorption of non-haem iron. In a study from Taiwan, Huang et al.[41] reported

31.7% adolescents with traceable aetiologies of iron deficiency were infected by *H. pylori*. With only 38.5% of occult blood tests of patients' stool testing positive, they found that *H. pylori* infection resulting in iron deficiency or IDA mainly influenced iron absorption versus bleeding. Eradication of *H. pylori* could be considered in cases that were refractory to iron supplementation and in the case of frequent relapses, assuming that other causes, such as coeliac disease and inflammatory bowel disease, have been excluded. Randomised, double-blind, and placebo-controlled trials of sufficient size and power should evaluate the long-term effect of *H. pylori* eradication in children with IDA. In children with refractory IDA, endoscopic examination may be necessary to rule out not only the presence of *H. pylori* but other aetiologies of anaemia.

Short Stature and Failure to Thrive

The available evidence regarding *H. pylori* infection and its effect on growth in children is also controversial.[8] Some cross-sectional analyses have indicated that *H. pylori*-infected children had subnormal growth retardation compared with non-infected children, but other studies did not support such findings.[8,27] Growth and failure to thrive (FTT) are important, complex issues, and, thus, assessing the association between *H. pylori* infection and growth is highly intricate. Some studies report that *H. pylori* may cause FTT, but the evidence is conflicting.[27]

Perri et al.[42] suggested that *H. pylori* infection is associated with growth delay in older Italian children, poor socioeconomic conditions, and household overcrowding. These findings are consistent with the hypothesis that *H. pylori* infection is one of the environmental factors capable of affecting growth. Based on the data of an observation cohort in southern Taiwan, Yang et al.[43] reported the *H. pylori*-infected children had significantly lower body weight (BW) and BMI than sex and age-matched controls at enrolment. After 1-year follow-up, the *H. pylori*-infected children had profoundly lower BW, BMI, and net BW gain than the non-infected children.[43] They also found *H. pylori* infection could be associated with decreased serum acylated ghrelin levels, BW, and height in children. Successful *H. pylori* eradication could restore ghrelin levels and the increase of BW and height in the infected children with growth retardation.[44]

However, in our recent study in northern Taiwan, we compared the *H. pylori* infection status in children with FTT and a matched control group.[24] There was no significant difference between infected and uninfected children with regard to BW, height, and BMI, and no association between FTT and *H. pylori* infection. Therefore, physicians should not overtreat *H. pylori*-infected children with FTT; the decision for eradication should be individualised and evaluated carefully.

In another cross-sectional study of Turkish children aged 4–16 years who underwent upper gastrointestinal endoscopy for RAP and dyspeptic complaints, Süoglu et al.[45] found that the effect of *H. pylori* infection on mean standard deviation scores of height for age was statistically insignificant after correction for breastfeeding, IDA, and socioeconomic level. After controlling for sociodemographic variables, the authors did not find significant differences in the nutritional parameters between infected and uninfected children. Taken together, the results of these studies that point to the presence or absence of an association between *H. pylori* and growth are subject to potential limitations. We conclude that future work in this area is needed to elucidate the importance of these factors.

ASTHMA, INFLAMMATORY BOWEL DISEASE, AND OTHERS

H. pylori infection does not always have negative consequences and some effects may be beneficial. A previous cross-sectional study revealed that adults <40 years of age with an *H. pylori* infection had an inverse correlation with asthma.[15] In addition, a beneficial relationship between *H. pylori* infection and other atopic diseases, obesity, and inflammatory bowel disease has also been reported.[16,46] Therefore, the decision to screen and eradicate *H. pylori* infection in children should be justified and individualised.

ANTIBIOTIC RESISTANCE

The current recommended first-line *H. pylori* eradication regimen is a clarithromycin-based triple therapy, including a proton pump inhibitor, and either amoxicillin or metronidazole. Such a regimen achieved an eradication rate of approximately 70–85% in the early 1990s;[5,47] however, eradication failures are concerning at the present time and they are likely to be more critical in the future,

given that global rates of antibiotic resistance are increasing and therapy for *H. pylori* infection is increasingly prescribed.[5] This is reflected in the most recent Maastricht Recommendations,[48] which state that susceptibility testing should be performed prior to therapy in regions with high clarithromycin resistance rates. Therefore, the consensus recommended that clarithromycin-based triple therapy should not be used empirically in the first-line therapy, when the local resistance rate is >15–20%.[48]

Although surveillance of antimicrobial-resistant *H. pylori* in each domestic area should be recommended and warranted, especially for clarithromycin and the commonly applied amoxicillin and metronidazole, only a few laboratories routinely grow *H. pylori* from biopsy specimens and perform antibiotic susceptibility testing on the isolates. For this reason, data on antibiotic resistance of *H. pylori* in children are sparse for many countries and geographic areas. The prevalence of bacterial antibiotic resistance is regionally variable and appears to be markedly increasing with time in many countries. In a study from Germany, overall resistance of *H. pylori* isolates, obtained from children and adolescents, to metronidazole, clarithromycin, and rifampicin, were 28.7%, 23.2%, and 13.3%, respectively, while resistance to amoxicillin was rare (0.8%).[49] Simultaneous resistance to metronidazole and clarithromycin was observed in 7.7% of the isolates and 2.3% were resistant to metronidazole, clarithromycin, and rifampicin. In Figure 3, global antibiotic resistant rates of *H. pylori* in children are shown.

In Taiwan, Lu et al.[50] recently investigated the changing antimicrobial susceptibility of *H. pylori* isolated from children over the past two decades. Conventional bacterial cultures were performed as the diagnostic standard. Minimal inhibitory concentrations of antibiotics were determined by an Epsilometer test. The overall antimicrobial resistant rates to clarithromycin, metronidazole, and levofloxacin were 23.4%, 20.3%, and 11.8%, respectively;[50] there was no recorded resistance to amoxicillin. In comparison, regarding the resistance rates of clarithromycin and metronidazole in the periods of 1998–2007 and 2008–2016, isolates in the latter period had higher resistance rates of clarithromycin (28.6% versus 17.2%) and metronidazole (25.7% versus 13.8%). The rates of resistance to clarithromycin and metronidazole have increased compared to levels a decade ago and this rapid evolution of antimicrobial resistance of *H. pylori* in children has led us to be more conscientious in the treatment of childhood *H. pylori* infection (Figure 3).

Due to the clinical importance of decreased eradication rates, regional variation in antibiotic resistance rates, and the marked increase over time of antibiotic resistance rates in the past decades, there is a critical need for determination of current rates at a local scale, and also in individual patients.

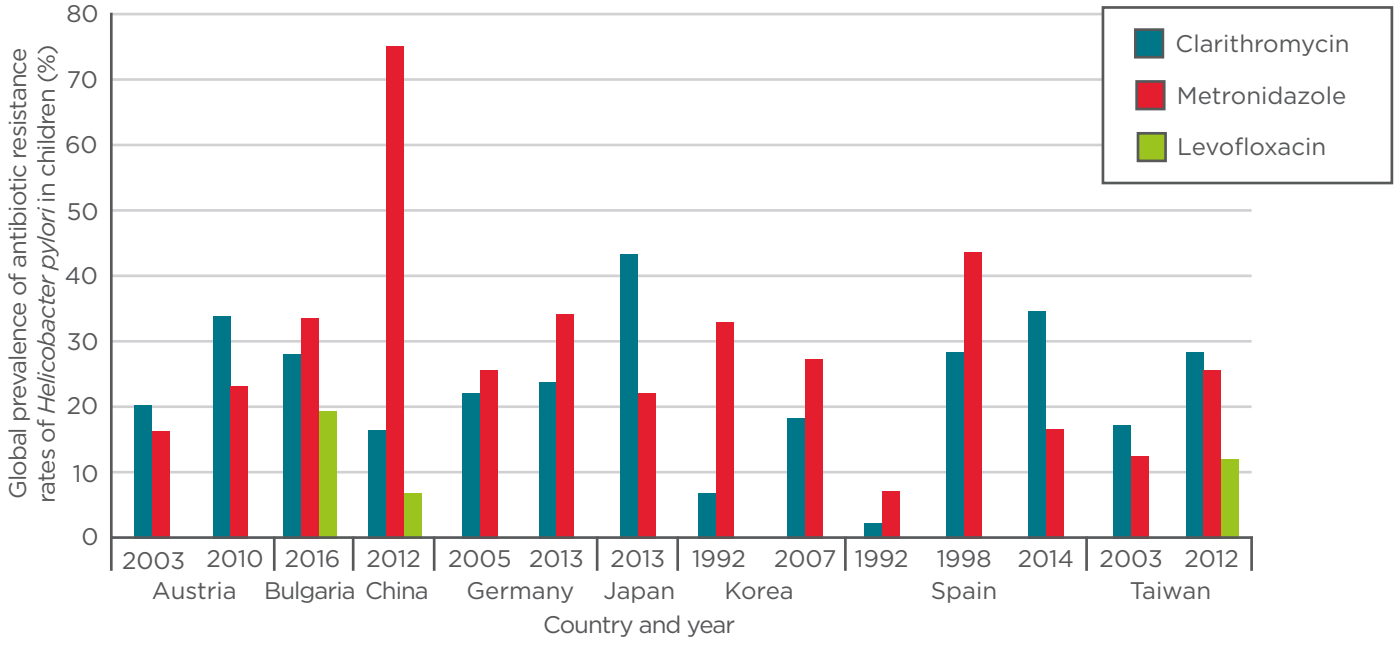

Figure 3: Global prevalence of antibiotic resistance rates of *Helicobacter pylori* in children.

Patient-specific tailoring of effective antibiotic treatment strategies may lead to reduced treatment failures and less antibiotic resistance.

CONCLUSION

As public hygiene and sanitation improves, the prevalence of *H. pylori* infection in children is declining in developed countries and clinical paediatricians need to re-evaluate when to test for *H. pylori* and whether to treat the infection.[29] However, we must be aware that the prevalence of *H. pylori* infection is still high in most countries worldwide, especially in developing countries, and optimal treatment of *H. pylori* infection in children has not yet been determined and will require further collaborative studies. Various regimens, including a proton pump inhibitor, have been used for treatment of *H. pylori* infection in adults,[5] but few studies concerning the clinical features, efficacy, and safety of treatment have been carried out in children. *H. pylori* treatment for children and adolescents seems safe, but further surveys evaluating adverse events need to be conducted.

With the propagation of public health education, advancement of diagnostic tools, and patient-specific tailoring therapeutic strategies, the prevalence and eradication failure rate of *H. pylori* infection in children should decrease in the near future, both in developed and developing countries.

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NUTRITIONAL DEFICIENCY AFTER SLEEVE GASTRECTOMY: A COMPREHENSIVE LITERATURE REVIEW

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ABSTRACT

Sleeve gastrectomy (SG) has been recognised as an effective procedure for the treatment of morbid obesity and associated comorbidities; however, the shortcomings of SG, such as staple line leak, haemorrhage, vomiting, and weight regain, have also been well-reported. An underestimated adverse effect of SG is nutritional deficiency (ND). While ND is a well-known complication of malabsorptive bariatric procedures, it can still occur after restrictive operations, including SG, yet its incidence and mechanism are still unclear. In an attempt to learn about the incidence and type of ND after SG we performed an organised literature search of electronic databases searching for articles that assessed the incidence and type of ND after SG. The median incidence of iron and zinc deficiency after SG was 8.8% and 18.8%, respectively. The majority of patients already had vitamin D deficiency preoperatively, with a median of 35.5% of patients still demonstrating vitamin D deficiency postoperatively. Comparing ND before and after SG, the incidence of iron and vitamin D deficiency declined postoperatively; in contrast, there was a tangible increase in the incidence of vitamin B1, B6, B12, and calcium deficiency. Vitamin B1 and B12 deficiencies were recorded in a median of 10.0% and 11.7% of patients, respectively, and were associated with neurologic manifestations in <1% of patients. Prevention of ND after SG requires proper recognition and correction of preoperative ND with immediate supplementation of trace elements and vitamins postoperatively, in addition to long follow-up.

Keywords: Nutritional deficiency (ND), review, sleeve gastrectomy (SG).

INTRODUCTION

Morbid obesity represents a substantial health crisis across the world with a rapidly increasing prevalence.[1] While lifestyle-altering measures, exercise programmes, and diet regimens manage to reduce excess body weight in some patients, bariatric surgery remains the ultimate treatment of choice for many patients who fail conservative measures. Bariatric procedures have achieved excellent results with regard to weight loss and improvement in comorbidities. However, various complications of bariatric procedures have been recognised, including anastomotic leakage, stenosis, bleeding, weight regain, and nutritional deficiency (ND).[2]

ND is a predictable complication after Roux-en-Y gastric bypass (RYGB) owing to the malabsorptive nature of the procedure.[3] Other restrictive procedures, including sleeve gastrectomy (SG), are also associated with ND. The prevalence, type, and mechanism of ND after SG are, however, not clearly understood.[4] This review aims to assess the magnitude of ND after SG and to explore the available preventative measures and treatment options.

SEARCH STRATEGY

A computerised, organised search of the English language scientific literature was conducted using the PubMed/Medline and Scopus databases. Studies reporting ND after SG performed on adult or adolescent patients with morbid obesity were included. The following keywords were used in the search process: "morbid obesity", "obesity", "sleeve gastrectomy","gastrectomy","restrictive","bariatric",

"nutritional deficiency", "nutrient deficiency", "micronutrient", "vitamin B", "vitamin D", "folic acid", "ferritin", "calcium", "iron", and "magnesium". The relevant articles and their list of references were screened for the type and incidence of ND after SG. After an initial screening of 332 articles and exclusion of irrelevant articles, editorials, and letters to the editors, 15 articles were considered eligible and were included in the review for analysis of the incidence of ND after SG (Table 1).

AETIOLOGY OF NUTRITIONAL DEFICIENCY AFTER SLEEVE GASTRECTOMY

Several nutritional consequences of SG have been recorded, including fluid deficits, vitamin and mineral deficiencies, iron deficiency anaemia, and metabolic bone disease.[5] The overall incidence of ND after SG is estimated to be 2.6%, according to a recent systematic review.[2]

The mechanism for ND after SG is multifactorial; it has been postulated that a pre-existing ND is already present in many patients preoperatively.[6] The unhealthy eating behaviour of patients with morbid obesity usually deprives these patients of essential vitamins and minerals. Pre-existing ND, if not corrected preoperatively, will continue postoperatively with the potential for further deterioration in micronutrient levels.[7-9]

Resection of the gastric fundus in SG can reduce the absorption of certain micronutrients, including iron, folic acid, and vitamin B12, akin to what occurs after partial gastrectomy for peptic ulcer disease.[10] In addition, the caloric restriction pattern of SG potentially contributes to folic acid, vitamin B1 and B6 deficiency, and hypocupraemia. Since hydrochloric acid is essential for iron absorption, and certain chelators such as ascorbic acid, sugars, and amino acids require acid pH to combine with soluble ferric iron to maintain it in soluble form at neutral or slightly alkaline pH, the reduced gastric acid secretion associated with SG impairs iron absorption and results in iron deficiency anaemia.[11,12] The hypoacidity of the remaining gastric sleeve also impairs the absorption of copper, resulting in haematologic and neurologic abnormalities. Another reason for vitamin B12 deficiency could be the reduced consumption of vitamin B12-containing food, particularly red meat, in addition to the diminished production of the intrinsic factor responsible for the bioavailability and absorption of vitamin B12.[13]

It is also important to note that other gastrointestinal disorders, including coeliac disease, *Helicobacter pylori* infection, and atrophic gastritis, may contribute to ND after SG. In particular, *H. pylori* can negatively impact the absorption of iron and vitamin B12, contributing to further deficiency of these nutrients after SG. Therefore, early diagnosis and eradication of *H. pylori* before SG can help reduce iron and vitamin B12 deficiency postoperatively.[14]

The type of patient can also influence the incidence of ND after SG, particularly vitamin D and calcium deficiency. It has been demonstrated that vitamin D and calcium metabolism is impaired in postmenopausal women, hence performing SG on this category of patients may lead to further deficiency of vitamin D and calcium and may warrant the administration of higher prophylactic doses of these elements postoperatively.[15]

LITERATURE REVIEW

Iron Metabolism

The impact of SG on iron metabolism was reported in 2009 by Hakeam et al.[16] who published information about 61 patients who underwent laparoscopic SG. Serum haemoglobin and iron indices, such as serum iron, transferrin saturation, ferritin, and soluble transferrin receptor (sTf-R), were measured preoperatively and at 6 and 12 months after SG. Iron deficiency and anaemia were recorded in three (4.9%) patients at the 12-month follow-up. Different patterns of iron deficiency were recognised; the first had an abnormally elevated sTf-R level, the second had low serum iron and transferrin saturation with high sTf-R, while the third had low levels of both ferritin and iron with reduced transferrin saturation. Furthermore, a significant increase in the incidence of vitamin B12 deficiency was noted (8.1% increased to 26.2% postoperatively), and a similar increase in folic acid deficiency was also observed (0% increased to 9.8% postoperatively).

Iron deficiency after SG can be explained partially by a marked reduction in iron absorption after SG. According to Ruz et al.,[17] a significant decrease in the absorption of haem-iron (23.9% reduced to 6.2%) and non-haem-iron (11.1% reduced to 4.7%) was recorded 12 months after bariatric surgery, including SG. This observation indicates a need for an effective increase in iron supplementation after SG to prevent iron-status impairment.

Table 1: Incidence of nutritional deficiency after sleeve gastrectomy.

Study	Type of study	Number of patients	Iron deficiency (%)	Anemia (%)	Calcium deficiency (%)	Zinc deficiency (%)	Magnesium deficiency (%)	Vitamin B1 deficiency (%)	Vitamin B6 deficiency (%)	Vitamin B12 deficiency (%)	Vitamin D deficiency (%)	Folic acid deficiency (%)	Hypoalbuminaemia (%)	Follow-up in months
Hakeam et al.[16] 2009	Prospective	61.0	4.9	4.9	NA	NA	NA	NA	NA	26.2	NA	9.8	NA	12
Sallé et al.[18] 2010	Prospective	33.0	25.0	NA	NA	18.8	NA	NA	NA	NA	NA	NA	0.0	12
Aarts et al.[7] 2011	Prospective	60.0	43.0	26.0	0.0	NA	NA	11.0	0.0	9.0	39.0	15.0	15.0	12
Ruiz-Tovar et al.[19] 2012	Retrospective	30.0	3.3	NA	NA	NA	NA	NA	NA	NA	3.3	NA	NA	24
Moore and Sherman[21] 2014	Prospective	60.0	NA	NA	NA	NA	NA	NA	NA	NA	27.3	NA	NA	3
Damms-Machado et al.[11] 2012	Prospective	54.0	4.3	NA	4.3	NA	NA	NA	17.2	17.2	70.4	13.8	NA	12
Van Rutte et al.[9] 2014	Prospective	200.0	18.5	6.5	2.0	5.0	3.0	9.0	4.0	11.5	36.0	12.5	0.5	12
Ben-Porat et al.[24] 2015	Retrospective	77.0	27.7	20.0	NA	NA	NA	NA	NA	16.7	93.6	21.4	NA	12
Belfiore et al.[25] 2015	Retrospective	47.0	8.8	NA	NA	32.4	NA	17.7	NA	6.0	11.8	11.8	NA	6
Al-Mulhim[26] 2016	Prospective	112.0	7.1	6.25	9.8	NA	2.7	NA	NA	14.3	8.9	6.25	NA	12
Saif et al.[27] 2012	Retrospective	30.0	0.0	28.6	0.0	14.3	0.0	30.8	NA	0.0	42.0	0.0	5.5	60
*Pellitero et al.[13] 2017	Prospective	51.0	NA	4.0	NA	NA	NA	0.0	0.2	0.0	35.0	0.0	NA	60
Gehrer et al.[28] 2010	Prospective	50.0	18.0	NA	0.0	34	NA	0.0	0.0	18.0	32.0	22.0	4.0	36
Alexandrou et al.[29] 2014	Prospective	40.0	30.0	54.2	NA	NA	NA	NA	NA	5.0	56.3	20.0	NA	48
Kheniser et al.[33] 2017	Retrospective	50.0	6.0	49.0	NA	NA	NA	NA	NA	12.0	NA	NA	NA	48
Median (range)	–	907.0	8.8 (0.0–43.0)	20.0 (4.0–54.0)	1.0 (0.0–9.8)	18.8 (5.0–34.0)	2.7 (0.0–3.0)	10.0 (0.0–30.8)	0.2 (0.0–17.2)	11.7 (0.0–26.2)	35.5 (3.3–93.6)	12.5 (0.0–22.0)	4.0 (0.0–15.0)	12 (3–60)

*Hypocupraemia increased from 0.5% to 9.8%.
NA: not available.

Zinc Metabolism

Sallé et al.[18] concluded that zinc deficiency is a frequent, yet underestimated, problem after bariatric surgery. Zinc deficiency was found to be less frequent after SG compared to RYGB and biliopancreatic diversion. Among 33 patients who underwent SG, 18.8% suffered zinc deficiency 1 year postoperatively compared to 6.5% before surgery. The mean serum level of zinc showed a non-significant decrease on follow-up. The incidence of patients with iron deficiency increased from 21.7% preoperatively to 25.0% at 1 year after SG; the authors attributed the increased deficiency to either inadequate protein intake, a defect in the compensatory mechanism of the gut and liver, or insufficient intake of dietary zinc.

Aarts et al.[7] emphasised that patients after SG are at serious risk of developing ND because of inadequate intake and uptake of micronutrients and nutrients. Among 60 patients, 43% developed iron deficiency, 39% suffered from vitamin D deficiency, 26% developed anaemia, 15% had folic acid deficiency, 15% developed hypoalbuminaemia, and 9% had vitamin B12 deficiency.

Calcium and Vitamin D Metabolism

The mid-term effect of SG on calcium and vitamin D metabolism was investigated by Ruiz-Tovar et al.[19] on 30 females. The incidence of vitamin D deficiency declined from 96.7% preoperatively to 3.3% at 1-year postoperative follow-up. One patient had hypoalbuminaemia and another had folic acid deficiency before SG; both patients had normal serum albumin and folic acid levels postoperatively. Serum levels of vitamin B12, vitamin D, folic acid, and iron considerably increased at 24 months postoperatively compared to a modest increase in serum levels of albumin, zinc, and calcium. This study was the first of its kind to report increased vitamin D levels after bariatric surgery, namely SG. A plausible explanation for this phenomenon was that the study was conducted in Spain, which has a higher sunlight exposure than North America and northern Europe where the previous studies were undertaken. According to the authors, patients were encouraged to practice outdoor activities to enhance physical performance that helped increase exposure to sunlight.

Parallel to their previous study, Ruiz-Tovar et al.[20] investigated changes in bone mineral density (BMD) at 1 and 2 years post SG. A statistically significant increase in the BMD values of the spine was noted at both follow-up points (5.7% increase at 1 year and 7.9% increase at 2 years). Furthermore, a direct correlation was observed between BMD and vitamin D increase. Moore and Sherman[21] suggested that vitamin D deficiency after bariatric surgery, including SG, is caused by reduced food intake. The authors advocated a daily supplementation with 2,000 IU of vitamin D3 and 1,500 mg calcium citrate; they found this protocol successful in reducing the incidence of vitamin D deficiency from 54.5% preoperatively to 27.4% 3 months after SG.

Lanzarini et al.[22] advocated that "Patients undergoing bariatric surgery should receive high-dose vitamin D supplementation independently of the surgical technique". Patients who underwent SG or RYGB were administered 400 IU/day of 25(OH)D with additional supplementation of 16,000 IU of vitamin D3 every 2 weeks if 25(OH)D serum levels were <30 ng/mL. Normal vitamin D levels were recorded in 69% of patients that received high-dose vitamin D supplementation, compared to 48.3% in the group that received the regular dose of the vitamin. This recommendation was supported by the conclusion of a randomised trial[23] that a supplementation of 80 µg/day of oily vitamin D3 effectively prevents vitamin D deficiency as well as to treat pre-existing deficiencies after SG.

Comparing Nutritional Deficiency Before and After Sleeve Gastrectomy

Damms-Machado et al.[11] compared pre and postoperative nutritional status after SG. At 1 year postoperatively, the incidence of vitamin D and iron deficiency declined from 83.0% to 70.4%, and from 29.0% to 4.3%, respectively. Conversely, the incidence of vitamin B6, vitamin B12, and folic acid deficiency increased from 11.1% to 17.2%, 9.3% to 17.2%, and 5.5% to 13.8%, respectively. While none of the patients had calcium deficiency preoperatively, 4.3% of patients had low serum calcium levels postoperatively.

Van Rutte et al.[9] also assessed ND before and 1 year after SG, and noted that the incidence of anaemia increased from 5.0% to 6.5%, whereas iron deficiency declined from 38.0% to 18.5%. Calcium deficiency increased from 0.5% to 2.0%, and magnesium deficiency from 2.0% to 3.0%. The incidence of phosphate deficiency decreased from 14.0% to 3.5%, whereas zinc deficiency increased from 0.0% to 5.0%. Folate deficiency declined from 24.0% to 12.5% and vitamin D from

81.0% to 36.1%, while vitamin B1 increased from 5.5% to 9.0% and vitamin B6 from 3.0% to 4.0%. The incidence of vitamin B12 deficiency remained the same both pre and postoperatively, equal to 11.5%.

Conversely, Ben-Porat et al.[24] found the effect of SG on ND at 1 year postoperatively to be modest. The incidence of anaemia, low ferritin levels, and vitamin B12 deficiency increased from 11.4%, 8.3%, and 11.7% before surgery to 20.0%, 11.1%, and 16.7% postoperatively, respectively. Conversely, iron deficiency decreased from 40.4% to 27.7%, folate deficiency from 40.5% to 21.4%, and vitamin D deficiency from 97.9% to 93.6%. Preoperative deficiencies of haemoglobin, folate, and B12 proved to be significant predictors for deficiencies 1 year after SG. The study concluded that proper recognition of preoperative ND alongside tailoring a specific supplemental programme for each individual should prevent postoperative ND.

Belfiore et al.[25] used bioelectrical impedance analysis to assess changes in body composition after SG. The energy intake exhibited a remarkable decrease after SG that was associated with marked changes in body composition demonstrated as a decrease in fat-free mass and fat mass 3 months postoperatively. With further follow-up, the fat-free mass loss slowed down whereas the decrease in fat mass continued for 6 months postoperatively. Iron deficiency decreased from 14.9% to 8.8%, vitamin B12 from 10.7% to 6.0%, folate deficiency from 19.1% to 11.8%, and vitamin D deficiency from 31.9% to 11.8%. In contrast, vitamin B1 deficiency increased from 0.0% to 17.7%, and zinc from 4.3% to 32.4%.

Al-Mulhim[26] described vitamin and ND after SG as a common phenomenon. The incidence of anaemia declined from 24.0% to 6.25%, iron deficiency from 11.6% to 7.1%, vitamin D deficiency from 60.0% to 8.9%, and magnesium from 6.2% to 2.7%. In contrast, the percent of patients with folate, vitamin B12, and calcium deficiency increased from 0.9%, 1.8%, and 0.0% to 6.25%, 14.3%, and 9.8%, respectively. The author devised a set of important recommendations to prevent ND after SG, including correction of preoperative ND, sufficient supplementation immediately after SG, and long follow-up.

Long-Term Effects of Sleeve Gastrectomy

The long-term influence of SG on nutrient status was studied by Saif et al.[27] in 82 patients with morbid obesity. At 5-year follow-up, vitamin D deficiency, vitamin B1 deficiency, low serum haemoglobin levels, hypoalbuminaemia, and zinc deficiency were recorded in 42.0%, 30.8%, 28.6%, 5.5%, and 14.3% of patients, respectively. No patients were recorded to have either iron, calcium, or magnesium deficiency at 5-year follow-up. Roughly 43.0% of patients reported taking supplements 3 years after SG and this percentage increased to 63.3% at Year 5.

Pellitero et al.[13] evaluated long-term status of vitamins and micronutrients after SG; 176 patients were prospectively followed for up to 5 years after surgery. The incidence of anaemia declined from 23.9% to 4.0%, vitamin B12 deficiency from 6.9% to 0.0%, folic acid deficiency from 6.5% to 0.0%, vitamin D deficiency from 73.0% to 35.0%, vitamin B1 deficiency from 3.4% to 0.0%, and vitamin B6 deficiency from 12.0% to 0.2%. Conversely, hypocupraemia increased from 0.5% preoperatively to 9.8% 5 years postoperatively, whereas none of the patients had selenium deficiency neither before nor after SG.

Comparing Sleeve Gastrectomy and Roux-en-Y Gastric Bypass Regarding Postoperative Nutritional Deficiency

Gehrer et al.[28] compared ND after SG with RYGB in 136 patients. The incidence of ND at 1 year postoperatively was generally less after SG than RYGB (34% versus 37% for zinc; 18% versus 28% for iron; 4% versus 8% for albumin; 32% versus 52% for vitamin D; and 18% versus 58% for vitamin B12) except for folate deficiency which was higher after SG than RYGB (22% versus 12%). Patients in both groups exhibited normal serum levels of calcium, vitamin B1, and vitamin B6. ND after SG was easily treated with nutritional supplementation in the form of intramuscular cyanocobalamin, oral folic acid therapy, intravenous therapy with iron(III)-hydroxide sucrose or oral administration of iron(II)-glycine sulphate, oral zinc gluconate 30 mg therapy, and oily suspension of cholecalciferol (300,000 IE).

Alexandrou et al.[29] compared the long-term influence of SG and RYGB on the micronutrient levels and found both procedures to be associated with significant ND. At 4-year follow-up, the incidence of vitamin B12 deficiency, anaemia, and iron deficiency was lower after SG compared to RYGB (5.0% versus 42.1%; 54.2% versus 64.3%; and 30.0% versus 36.4%, respectively), whereas folate and vitamin D deficiencies were more frequently detected after SG than RYGB (20.0% versus 18.4%, and 56.3% versus 39.6%,

respectively). It is important to note that there were no significant differences in postoperative ND among the two procedures with exception to vitamin B12 deficiency.

A meta-analysis of nine studies that assessed ND after SG and RYGB[30] concluded that both operations had similar odds for developing anaemia and iron deficiency postoperatively; however, RYGB had higher odds for developing postoperative vitamin B12 deficiency than SG (odds ratio: 3.5; p=0.001). Since vitamin B12 deficiency is more frequent after RYGB, Majumder[31] proposed that while patients undergoing SG need vitamin B12 supplementation postoperatively, they may be maintained on a lower daily dose of vitamin B12, lower than the regular dose prescribed for patients with RYGB.

According to Brandão et al.[32] both RYGB and SG had no influence on the serum level of vitamin A and visual function postoperatively. Conversely, Kheniser et al.[33] demonstrated that a significantly higher number of SG patients developed postoperative anaemia compared to RYGB patients (49% versus 23%; p=0.01). The percent of patients who had deficiencies in the mean corpuscular volume, haematocrit, transferrin, red blood cell folate level, iron, and vitamin B12 were higher after SG than RYGB.

Neurologic Complications

Micronutrient deficiency after SG may lead to neurologic manifestations as seen in vitamin B1 (thiamine) deficiency, which results in Wernicke's encephalopathy (WE). A systematic literature review[34] included 13 reports describing the occurrence of WE after SG with the majority of patients being female. Thiamine deficiency was attributed to gastric wall oedema and non-dietary compliance. The diagnostic triad of WE include ocular impairment and nystagmus, cerebellar dysfunction, and confusion in addition to severe polyneuropathy in some cases. WE usually responds to intensive therapy of thiamine with complete resolution of symptoms occurring within a few months.

Vitamin B1 deficiency can also result in beriberi, a condition that is associated with severe peripheral polyneuropathy characterised by sensory and motor losses. Durán et al.[35] reported a case of a young female who developed progressive paraesthesia and intense pain and loss of strength in her lower limbs disabling the patient from walking 6 weeks after SG. The patient showed a slow but steady response to parenteral thiamine therapy. Three months later, the patient was discharged on vitamin supplementation and physiotherapy.

Another serious neurologic consequence of vitamin deficiency was reported by Sawicka-Pierko et al.[36] who presented the case of a middle-aged female who developed optic neuropathy 10 months after SG. The patient presented with bilateral decrease of visual acuity and a bilateral loss of visual field. A marked decrease in serum level of vitamin B12 was noted. Intramuscular injection of vitamin B12 managed to resolve the visual symptoms and tripled the serum vitamin B12 level within 1 week of therapy. The authors recommend that all patients receive long-term ophthalmological follow-up after SG.

Punchai et al.[37] reported neurologic manifestations including WE, paraesthesia, muscle weakness, abnormal gait, and polyneuropathy secondary to vitamin B deficiencies in 0.7% of patients after a median duration of 12 months. After nutritional supplementation, resolution of neurologic symptoms occurred in 85% of patients yet WE was not fully reversible.

LIMITATIONS

This review is limited by the relatively small number of studies included (Table 1). Furthermore, the majority of the studies measured the micronutrient level in the serum or plasma, not the whole blood, which may affect the reliability of these measurements; plasma contains coagulant factors that may interfere with accurate assessment of trace elements. In addition, most of the studies focussed on the changes in biochemical parameters after SG without elaborating on the clinical impact of these changes on the outcome of patients.

CONCLUSION

The median incidence of iron and zinc deficiency after SG was around 9% and 20%, respectively. The majority of patients already had vitamin D deficiency preoperatively due to sequestration of vitamin D in fat reserves; a median of 35.5% of patients still suffered vitamin D deficiency after postoperatively. Comparing ND before and after SG, the incidence of iron and vitamin D deficiency seemed to decline postoperatively. On the contrary, vitamin B1, B6, B12, and calcium deficiency showed a tangible increase. A deficiency in vitamin B1 and B12 was recorded in a median of 10.0% and 11.7% of patients, respectively, and was associated with neurologic manifestations in <1.0% of patients.

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UPCOMING EVENTS

Royal College of Physicians of Edinburgh (RCPE) 22nd Advanced Gastroenterology & Hepatology Course 2018 (Gastro Course)

25th–26th January 2018

Edinburgh, UK

This course focusses on providing trainees and consultants with the latest advances in the management and treatment of gastrointestinal and liver-related disorders. With expert speakers from all around Europe providing their knowledge on these specialist areas, the RCPE 22nd Gastro Course is the place to be this January. Be sure to book your place on this fantastic event before tickets sell out.

20th Düsseldorf International Endoscopy Symposium 2018

1st–3rd February 2018

Düsseldorf, Germany

This symposium brings together numerous pharmaceutical companies from the field of endoscopy, with representatives providing overviews of the latest updates in the treatment of gastrointestinal disorders. With the opportunity to quiz the experts, as well as lectures, live demonstrations, and 'snack with the experts' sessions, this event offers a unique chance to delve into the minds of some of the discipline's best and brightest.

13th Crohn's and Colitis Organisation Congress 2018 (ECCO 2018)

14th–17th February 2018

Vienna, Austria

The programme of the 13th ECCO Congress builds on the theme of "Science improving patients' lives", with particular emphasis surrounding the innovative therapeutic discoveries for inflammatory bowel diseases uncovered this last year. The congress aims to disseminate current research and ideas from across Europe, as well as advising on recent updates and providing an informative, thought-provoking, and thoroughly enjoyable experience for all those who attend.

Belgian Week of Gastroenterology 30th Annual Meeting 2018 (BWGE 2018)

21st–23rd February 2018

Antwerp, Belgium

Titled the "Number One" gastroenterology and hepatology event in Belgium, BWGE 2018 looks set to provide another year of exciting collaboration between scientific researchers and clinicians alike. Nutrition, ultrasonography, and nuclear medicine form just a few of the topics included across the 3-day event. A very special, traditional dinner and party will also be held on the Thursday evening, to create an event equally rich in scientific and networking opportunities.

German Society of Endoscopy and Imaging 48th Congress 2018 (DGE-BV 2018)

15th–17th March 2018

Munich, Germany

The DGE-BV 2018 seeks to bring together clinicians, researchers, and technical and engineering societies with the ultimate aim of improving endoscopy and imaging techniques. Included at the event will be an exciting live demonstration of an endoscopy procedure with brand-new technology. Particular attention will be paid to young researchers with the potential to become the forerunners of the field, as well as calls for abstracts with research focussing on the latest advances in gastroenterology.

Italian Society of Digestive Diseases 24th Congress 2018 (FISMAD 2018)

21st–24th March 2018

Rome, Italy

FISMAD 2018 promises a huge variety of topics at its 24th congress. This comprehensive event promises 4 days packed full of insightful and innovative talks and presentations on a wide range of hot topics, from inflammatory bowel diseases to new diagnostic and treatment techniques. Awards will also be presented to the best abstracts, celebrating the enormous variety and excellent quality of research on show.

United European Gastroenterology (UEG) Week 2018

20th–24th October 2018

Vienna, Austria

UEG Week 2018 is one of the many events members of the European Medical Journal will be attending in 2018 and we hope to see you there. With a myriad of research areas being covered, debate and collaboration will be flourishing over this enormous 5-day event. Special attention will be paid to the nurturing of young researchers, as well as to unique hands-on sessions designed to impart first-hand experience. As ever, Europe's largest gastroenterology event looks sure to thrill and delight.

Japanese Digestive Disease Week (JDDW) 2018

1st–4th November 2018

Kobe, Japan

JDDW 2018 will be combining special lectures from six Japanese societies that specialise in digestive disease medicine. Experts from each society will be presenting their own research and opinions on a variety of digestive disease-based topics, including non-alcoholic fatty liver disease management, Hepatitis virus infections, and pancreatic cancer, to name but a few. This huge event is the ideal opportunity for all those in the field to increase their knowledge of digestive disease innovations.

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