EMJ EUROPEAN MEDICAL JOURNAL

GASTROENTEROLOGY

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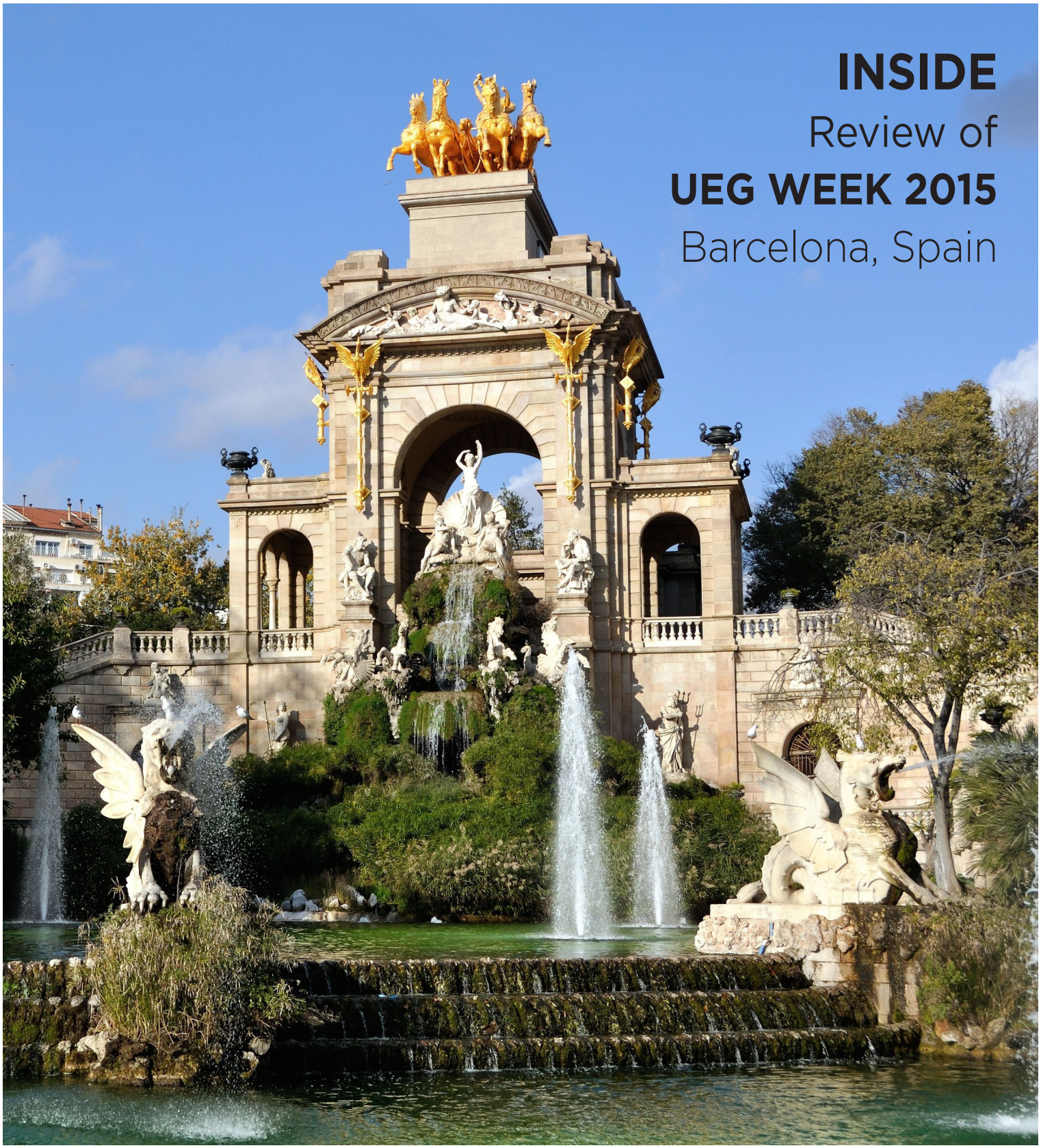

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UEG WEEK 2015

Barcelona, Spain

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Gastroenterology

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European Medical Journal
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Vol 4.1
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Welcome

Hello and a warm welcome to this edition of *European Medical Journal Gastroenterology*, an extensive guide to the latest in research and practice in gastroenterological medicine.

In this edition we report on the events of United European Gastroenterology (UEG) Week 2015, which took place from 24th–28th October in Barcelona, Spain. This historic city, with its many academic institutions and cultural landmarks, was a perfect setting for the event. Alongside this we bring you a number of interviews from the forefront of clinical practice, a selection of pioneering abstract reviews, and some groundbreaking peer-reviewed research.

Over 13,000 specialists, experts, and students descended upon Barcelona for the biggest UEG Week yet, and EMJ was there to capture the most important highlights. Topics ranged across the whole spectrum of gastroenterological science and medicine. Some particularly stand-out presentations included themes such as: personalised medicine in colorectal cancer, obesity and child development, and the World Health Organization's new classification of processed meats as carcinogens.

This eJournal also includes some innovative new research in the form of abstract reviews and papers. Our abstract reviews cover topics ranging from hepatitis C treatment through to the screening and diagnosis of coeliac disease. Building on this, we have a number of captivating papers that summarise some of the most influential and impactful research from this year. Cuomo and colleagues present the latest in the management of diverticulitis and how to best prevent recurrence with a unique look at the complex evaluation methods required. Spicak and Hucl review the use of endoscopic retrograde cholangiopancreatography and the technical demands that have arisen with the evolution of this technique. Meanwhile, we have an update on evidence and guidelines for the treatment of cystic pancreatic lesions by Salvia et al. Alongside these we have many other cutting-edge papers, containing theory that we hope will aid you in your current work.

As we come to the end of another fantastic year, we would like to thank you, our readership, for your ongoing support and interest. We would also like to extend our thanks to the editorial board, who provide an invaluable service to this publication. We continue to be fascinated by the plethora of research and innovation that we see here, and we have high hopes that this will continue into the new year. We hope that *EMJ Gastroenterology* can provide you with the best new information for your practice and we look forward to seeing you in 2016.

Spencer Gore

Director, European Medical Journal

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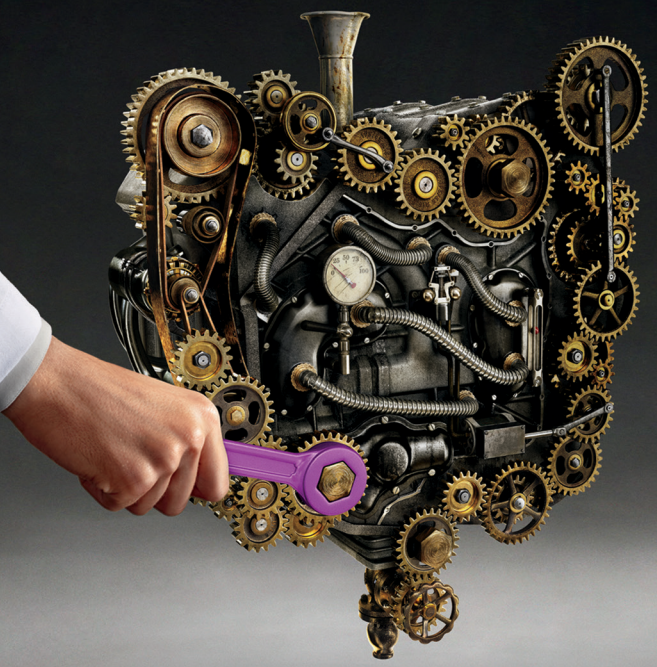
Introducing Entyvio®: the first and only gut-selective biologic for patients with ulcerative colitis (UC) or Crohn's disease (CD)[1]

TREAT WITH PRECISION



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2. Entyvio Prescribing Information. Takeda Pharmaceuticals America, Inc. 2014.

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Presentation: 300 mg powder for concentrate for solution for infusion. **Indication:** Adult patients with moderately to severely active ulcerative colitis(UC)/Crohn's disease (CD) who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist. **Dosage & Administration:** Treatment should be initiated and supervised by a specialist healthcare professional experienced in diagnosis and treatment of ulcerative colitis or Crohn's disease. Patients should be monitored during and after infusion in a setting equipped to manage anaphylaxis. Ulcerative colitis: Recommended dose regimen 300mg administered by intravenous infusion over approximately 30 minutes at 0, 2, 6 weeks and 8 weeks thereafter. Reconsider treatment if no evidence of therapeutic benefit at week 10. If patients experience a decrease in response, they may benefit from increased dosage frequency to 300mg every 4 weeks. Corticosteroids may be reduced/discontinued in patients who respond to treatment with Entyvio. If therapy is interrupted and needs to be restarted, Entyvio dosing every 4 weeks may be considered. Crohn's disease: Recommended dose regimen is 300mg administered by intravenous infusion over approximately 30 minutes at 0, 2, 6 weeks and 8 weeks thereafter. Patients who have not shown evidence of therapeutic benefit may benefit from a dose at week 10. Continue therapy every 8 weeks from week 14 in responding patients. Therapy should be discontinued if no evidence of therapeutic benefit is observed at week 14. If therapy is interrupted and needs to be restarted, Entyvio dosing every 4 weeks may be considered. Paediatric populations: No data available in children aged 0-17 years. Not recommended. Elderly patients: No dosage adjustment required. Renal or hepatic impairment: Entyvio has not been studied in these populations. No dose recommendation can be given. **Contraindications:** Hypersensitivity to Entyvio or any of the excipients. Active infections such as tuberculosis (TB), sepsis, cytomegalovirus, listeriosis and opportunistic infections such as Progressive Multifocal Leukoencephalopathy (PML). **Warnings and Precautions:** Patients should be observed continuously during infusions for signs/symptoms of hypersensitivity reactions. Patients should continue to be observed for two hours following infusion completion for the first two infusions and one hour for subsequent infusions. Infusion-related reactions (IRR): Hypersensitivity reactions have been reported, the majority were of mild to moderate severity. Discontinue treatment if anaphylaxis or other serious allergic reactions occur and institute appropriate treatment. In mild to moderate IRR, slow or interrupt infusion. Consideration for pre-treatment with antihistamine, hydrocortisone and/or paracetamol should be given prior to next infusion, for patients with history of mild/moderate IRR to Entyvio. Infections: Not recommended in patients with active, severe infections until infections are controlled. Consider withholding in patients who develop severe infection while on treatment with Entyvio. Before initiating treatment, patients must be screened for TB. If latent TB is diagnosed, anti-tuberculosis appropriate treatment must be initiated prior to Entyvio treatment. Progressive Multifocal Leukoencephalopathy (PML): No cases were observed in Entyvio clinical trials, but John Cunningham (JC) virus infection resulting in PML and death has occurred in patients treated with other integrin receptor antagonists and systemic immunosuppressive agents. A risk of PML cannot be ruled out. Monitor patients for any new or worsening neurological signs/symptoms. Malignancy: Underlying increased risk of malignancy in UC and CD. Immunomodulatory products may increase risk. Prior and concurrent use of biological products: No clinical data available for Entyvio use in patients previously treated with natalizumab or rituximab. Patients previously exposed to natalizumab should wait at least 12 weeks prior to initiating Entyvio therapy. Entyvio not recommended for concomitant use with biologic immunosuppressants as no clinical data available. Live and oral vaccines: Patients may continue to receive non-live vaccines. Patients recommended to be up-to-date with all appropriate immunisations prior to initiating Entyvio. Live vaccines may be administered concurrently only if benefit clearly outweighs risk. **Interactions:** No interaction studies performed. Concomitant administration of corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, and methotrexate) and aminosalicylates did not have a clinically meaningful effect on Entyvio pharmacokinetics. **Fertility, pregnancy and lactation:** Women of child-bearing potential should use adequate contraception and continue for at least 18 weeks after last Entyvio treatment. Since maternal antibodies are excreted in breast milk, decision whether to discontinue breast-feeding or discontinue/abstain from Entyvio should be made according to relative benefit to child of breast-feeding or to mother of Entyvio. **Undesirable Effects:** Very Common (≥1/10): nasopharyngitis, headache, arthralgia. Common (≥1/100, <1/10): bronchitis, gastroenteritis, URTI, influenza, sinusitis, pharyngitis, paraesthesia, hypertension, oropharyngeal pain, nasal congestion, cough, anal abscess, anal fissure, nausea, dyspepsia, constipation, abdominal distension, flatulence, haemorrhoids, rash, pruritus, eczema, erythema, night sweats, acne, muscle spasm, back pain, muscular weakness, fatigue, pain in extremities, pyrexia. Other serious undesirable effects (≥1/1000 to <1/100): respiratory tract infection, infusion site reaction, infusion-related reaction. **Refer to the SmPC for details on full side effect profile and interactions. Basic NHS Price:** £2,050. **Legal Classification:** POM. **Marketing Authorisation:** EU/1/14/923/001 300mg powder for concentrate for solution for infusion. Takeda UK Ltd is responsible for sale and supply of Entyvio in the UK. Further information is available from Takeda UK Ltd. Building 3, Glory Park, Glory Park Avenue, Wooburn Green, Buckinghamshire, HP10 0DF. Tel: 01628 537900 Fax: 01628 526617. **PI Approval Code:** UK/EYV/1508/0174. **Date of revision:** September 2015.

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Foreword

Prof Marco J. Bruno

Professor and Head of the Department of Gastroenterology and Hepatology, Erasmus Medical Center, Netherlands.

Dear Colleagues,

It is my esteemed pleasure to present to you the latest edition of *European Medical Journal Gastroenterology*. This open access publication provides our readers with high-quality peer reviewed articles highlighting exciting areas and developments in the field of gastroenterology and hepatology.

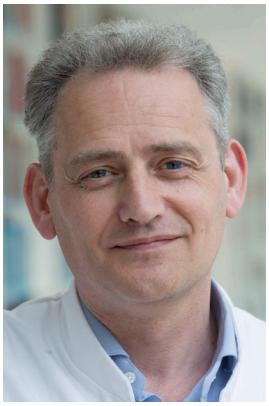
“I would also like to direct your attention to other ways to keep up to date with our specialty field and invite you to subscribe and join one of the journal’s social media channels either through Facebook, Twitter, or LinkedIn.”

A very successful 2015 edition of the United European Gastroenterology (UEG) Week is only a few weeks behind us. Clinicians and scientists from all over the world gathered in Barcelona, Spain, and were updated with the latest findings and developments in our specialty field. Importantly, this year’s UEG Week also excelled in using novel and interactive formats to teach the current standards in diagnosis and therapy.

In this issue of *EMJ Gastroenterology* we present to you a range of featured articles that touch upon important and challenging aspects pertaining to gastroenterological and hepatologic diseases with which we as professionals are faced on a daily basis when providing care to our patients. These articles aim to provide you with concise, well-balanced, and up-to-date information on a wide range of topics including paediatric liver diseases, modalities for dysplasia monitoring in Barrett´s oesophagus, evidence-based management of ascites, management of diverticulitis, the current treatment recommendations for *Helicobacter pylori* infection, and the clinical relevance of cystic pancreatic lesions. Moreover, we also feature an article on a subject close to my heart; ‘Perfect/failed ERCP: what makes the difference’.

I am sure that this edition of *EMJ Gastroenterology* will feature something to your liking and interest. I would also like to direct your attention to other ways to keep up to date with our specialty field and invite you to subscribe and join one of the journal’s social media channels either through Facebook, Twitter, or LinkedIn. I wish you much enjoyment in reading though this edition.

Kind regards,



Marco J. Bruno

Professor and Head of the Department of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, Netherlands; Council Member and Treasurer of the European Association of Gastroenterology, Endoscopy & Nutrition; Past Council Member of United European Gastroenterology (UEG); Past Chairman of the Education Committee of UEG and the Dutch Pancreatitis Study Group.

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Available Now
EMJ Hepatology 3.1 2015

Includes a selection of the latest articles for hepatology.

Featured articles:

Editor's Pick: Non-Alcoholic Fatty Liver Disease - Changing the Prevalence of Liver Cancer?

- Benedetta Campana et al.

Alcohol Dependence and Alcoholic Liver Disease

- Karl Mann and Sebastian Mueller

The Liver Meeting 2014: Summary of Presentations on Genotype 3 HCV Infection from the 65th Annual Liver Meeting of the American Association for the Study of Liver Diseases (AASLD), held in Boston, MA, USA, on 7th-11th November, 2014

- Markus Peck and Stanislas Pol

Definitions of Acute-On-Chronic Liver Failure: The Past, the Present, and the Future

- Roland Amathieu and Ali Al-Khafaji

Hepatic-Based Inborn Errors of Metabolism

- Tormod Lund

Metabolic Syndrome in Paediatric Population: Is it Time to Think Back on Diagnosis Criteria?

- Claudia Della Corte et al.

Paediatric Metabolic Conditions of the Liver

- Elroy P. Weledji

Diagnosis and Management of Occult Hepatitis B Virus Infection: A Short Review

- Javier Martínez González et al.

Occult HBV Infection Reactivation in Non-Hodgkin's Lymphoma: An Update on Prevalence and Management

- Valerio Rosato et al.

Homozygosity for the C282Y Substitution in the *HFE* Gene: The Incomplete Penetrance and Variable Expressivity

- Dilum Ekanayake et al.

How I Diagnose and Treat Acute (Fulminant) Liver Failure

- Dr Kenneth J. Simpson

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UEG ANNUAL CONGRESS 2015

GRAN VIA VENUE,
BARCELONA, SPAIN
24TH-28TH OCTOBER 2015

Welcome to the *European Medical Journal* review of the 23rd United European Gastroenterology Week

The world renowned city of Barcelona played host to UEG Week for the second time during the 2015 event, and it proved to be a momentous occasion. Barcelona is a seaside city filled with glorious culture and architecture. It is also home to one of the world's biggest football clubs, FC Barcelona, who play their home matches at the famous 'Camp Nou', which has the largest capacity of any stadium in Europe.

Against this backdrop, it was little surprise that over 13,200 participants from 114 countries around the world were in attendance. The event aims to improve standards of care in gastroenterology and promote an ever greater understanding of digestive and liver diseases among both the public and the medical community. In his welcome address, UEG President Prof Michael Farthing outlined the increasingly internationalist nature of UEG Week, and the inherent benefits of this: "Although UEG Week is a medical congress firmly based in Europe, we are delighted to welcome increasing numbers of participants from all over the world, including Asia, North and South America, the Middle East, and Africa. Presentation of new research from countries outside Europe enriches our programme and provides the opportunity for European investigators to develop new international research collaborations."

Awards were plentiful at the congress, with a number of gastroenterologists

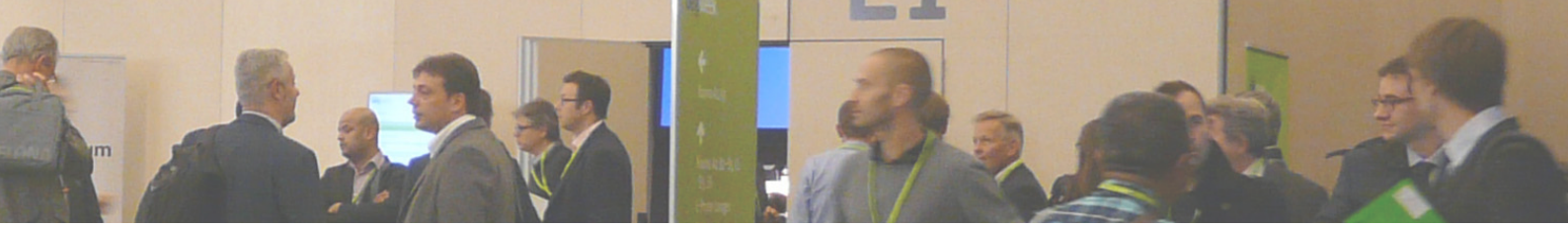
receiving recognition for their achievements in the field. Prof Jan F. Tack (Belgium) was the recipient of the UEG Research Prize, for his work entitled 'Role of nutrients and tastants in determining the gastric accommodation (GA) reflex and the control of meal volume tolerance in health and disease'. This prize is awarded for excellence in basic science, translational, or clinical research, and it must be shown that the awardee's research has had an impact in its field and has also been recognised internationally.

The UEG Lifetime Achievement Award, which recognises outstanding individuals whose pioneering and inventiveness throughout their careers have improved the Federation and inspired others, went to Prof Chris Hawkey (UK) this year. Additionally, the authors of the top five abstracts submitted to the congress were awarded €10,000 each to fund future research. The recipients of these awards were Dr Edmund Derbyshire (UK), Dr Alexander Kleger (Germany), Dr Daffolyn Rachael Fels Elliot (UK), Dr William J. Sandborn (USA), and Dr Angela Bureo Gonzalez (Netherlands).

Innovation was a key component of UEG Week 2015, demonstrated by the implementation of new interactive formats including the Posters in the Spotlight and Poster Champ Sessions. A particular highlight of the event was the UEG Week Hotspot, which took place in a circular studio and featured the most controversial sessions and high-profile debates in the field. Other notable sections of UEG Week included a presentation by Prof Thomas Knittel (Sweden) of a *post hoc* analysis of a Phase III trial investigating DIMS0150, a Toll-like receptor-9 agonist, in 131 patients with chronic, active, moderate-to-severe disease, as well as the results of a pilot study that assessed the use of a novel, simple endoscopic ultrasound-guided technique to measure portal pressure gradients, increases in which are a major complication of liver cirrhosis, which were presented by Dr Jason Huang (USA). Additionally, the results of a trial involving a novel endoluminal suturing system to aid endoscopic gastric restriction were reported by Dr Vincent Huberty (Belgium), and Dr Arthur Schmidt (Germany) presented the findings of a prospective, multicentre trial which suggests that full thickness resection is feasible with a novel over-the-scope device.

UEG Week 2015 was filled with many such fascinating studies, and the research that was on show is certain to enhance the knowledge and abilities of gastroenterological health professionals in their work and research. Next year's venue will be in Vienna, Austria, and we look forward to this next instalment with much anticipation.

"Presentation of new research from countries outside Europe enriches our programme and provides the opportunity for European investigators to develop new international research collaborations."



HIGHLIGHTS

Poor Diet During Pregnancy Increases Risk of Obesity in Offspring

INCIDENCE of obesity in children is increasing at an alarming rate, with a global increase of almost 40% in the number of obese children aged <6 years between 1990 and 2013, according to the World Health Organization. There is now mounting evidence that nutrition and lifestyle in the first 1,000 days of a child's life, including during pregnancy and the first 2 years of infancy, play a vital role in many aspects of future health of the child.

Childhood obesity is attributed to a combination of factors including the child's genetic make-up and the consumption of energy-dense food high in fat, sugar, and salt, alongside a lack of physical activity. Another key risk factor that has been identified is obesity in expectant mothers. Women who are overweight are much more likely to have overweight children than those with a normal weight before pregnancy, and evidence suggests that it may be possible for the increased likelihood of obesity and associated conditions such as coronary heart disease, insulin resistance, and diabetes to be transferred to subsequent generations. During a presentation at UEG Week 2015, Prof Berthold Koletzko, Professor of Pediatrics and Head of the Division of Metabolic Diseases and Nutritional Medicine, Dr. von Hauner Children's Hospital, University of Munich Medical Center, Munich, Germany, explained: "We know that a sedentary lifestyle and poor diet in pregnancy increase the risk of children becoming overweight and obese, but we now also think that babies in the womb can have their genetic make-up permanently altered depending on the mother's diet. Perhaps even more worryingly, these metabolic and epigenetic changes can be passed from generation to generation, which has major public health implications." Permanent, lifelong metabolic reprogramming in children with obese mothers is thought to occur due to exposure of the fetus to an excess of fuels such as glucose and fatty acids during a period of developmental plasticity.

Experts from UEG are now working to convince expectant mothers and women of childbearing age to maintain physical activity and a balanced diet, which can be effective in reducing the birth weight of babies and therefore preventing permanent damage to their

child's health. Following birth, improved post-natal feeding is another effective tool for obesity prevention. In a study of 1,700 infants from 5 European countries, Prof Koletzko and his team demonstrated that infants bottle-fed of commonplace high-protein formula had a higher risk of rapid weight gain during infancy and obesity in early age than infants who were breast-fed or bottle-fed using a reduced-protein intervention formula. Breast-fed infants were 20% less likely to be overweight and 25% less likely to become obese during infancy than those receiving high-protein formula. Infants on the low-protein diets were also significantly leaner at 6 years of age, with obesity seen in only 3% of those that were breast-fed and 4% in those who received the reduced-protein formula, compared with 10% of children who received the high-protein formula.

Prof Koletzko summarised in a UEG press release dated 26th October: "These results demonstrate that improving nutrition and lifestyle during the first 1,000 days of life, including pregnancy and the first 2 years of childhood, provide enormous opportunity for improving lifelong health and well-being."

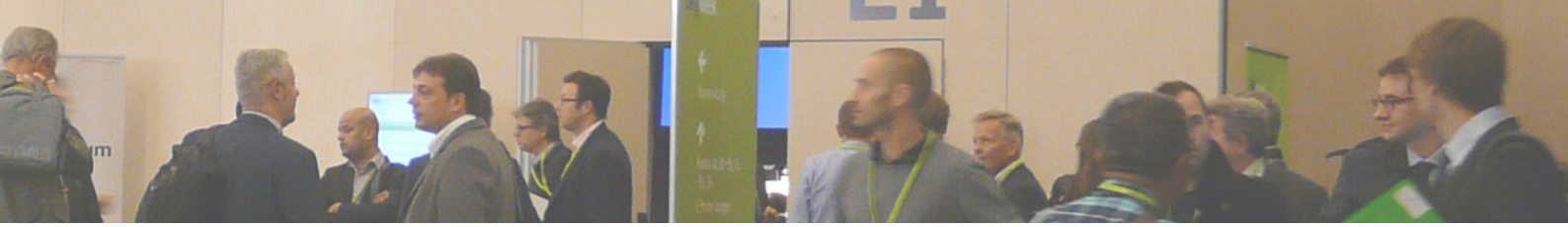
"We know that a sedentary lifestyle and poor diet in pregnancy increase the risk of children becoming overweight and obese, but we now also think that babies in the womb can have their genetic make-up permanently altered depending on the mother's diet."

Greater Risk of Colorectal Cancer with Increasing Weight

EXCESS body weight and an expanding waist size increase the risk of colorectal cancer (CRC), according to new evidence presented at UEG Week 2015. CRC is the third most commonly diagnosed cancer in both men and women, as well as the third leading cause of cancer death.

The new data show an overall increase in relative risk of CRC of 18% for each 5 kg/m^2 increase in body mass index (BMI), while the risk was increased by 60% in men who gained at least 10 cm in waist circumference over 10 years. Furthermore, data from patients with Lynch syndrome (LS) show that the risk of CRC in those who are overweight is double that of the general population, and obese LS patients are twice as likely to develop CRC as those within the normal weight range. The greater risk of CRC in LS patients has been demonstrated previously and is due to an inherited defect in one of the genes responsible for DNA repair.

The new findings were presented by Prof John Mathers, Professor of Human Nutrition, Institute of Cellular Medicine, Newcastle University, Newcastle Upon



Tyne, UK, who stated in a UEG press release dated 26th October: "This increased cancer risk may be due to persistent inflammation in people with obesity." He went on to add: "There is now compelling evidence that improved lifestyle, particularly better dietary choices, and being more physically active can help to prevent obesity and this will lower bowel cancer risk."

The researchers hope that, in light of the study results and in line with the drive to improve the lifestyle of the general public, further information and assistance can now be given to help people stay healthy and lower their risk of developing CRC, as well as other health problems. Further studies are required to develop ways of reducing the CRC risk in people who are already overweight, with the present study finding that the use of aspirin in LS patients lowered their excess risk of CRC, possibly due to the drug's anti-inflammatory effects. "This is a very intriguing finding," said Prof Mathers, "which suggests that dietary and other anti-inflammatory agents might be beneficial in reducing CRC risk in people with obesity."

"There is now compelling evidence that improved lifestyle, particularly better dietary choices, and being more physically active can help to prevent obesity and this will lower bowel cancer risk."

"Bowel cancer is strongly associated with age, obesity, and diet – and is driven by inflammation. We can now give the public clear advice on the benefits of staying physically active, eating a healthy diet, and avoiding weight gain to lower CRC risk as we get older," Prof Mathers concluded. It is hoped that these findings and their implications will ignite a desire for people to play an active role in their health.

Prevention of Many GI Cancers May Be Possible with Risk Profiling

OFTEN described as a scourge of Europe, cancers of the gastrointestinal (GI) tract are often diagnosed too late for effective treatment. This fact has led to the improvement of bowel cancer screening programmes in most European countries; however, the remainder of GI cancers are still a problem that, on the whole, is not being addressed. It is therefore unsurprising that the experts who gathered at UEG Week 2015 have declared a need for better risk profiling in all GI cancers, in order to further the development of targeted approaches to their screening and prevention.

Prof Rebecca Fitzgerald, Addenbrooke's Hospital and the University of Cambridge, Cambridge, UK, has suggested a five-tier model of

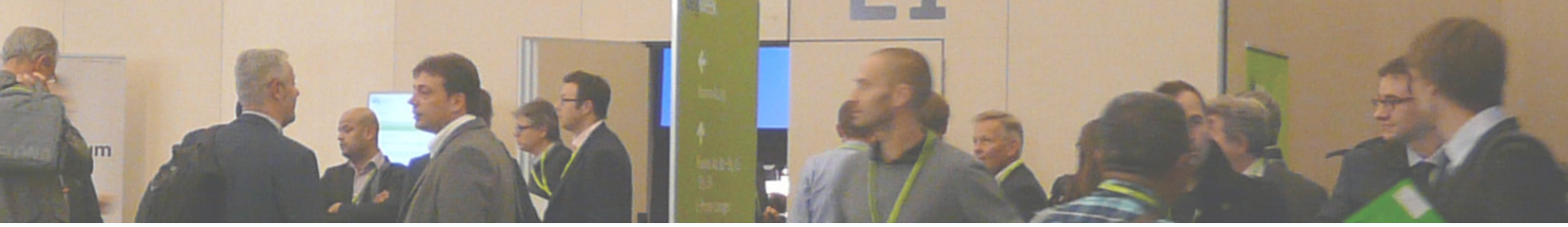
precision prevention, screening, and preventative approaches in relation to the most common type of oesophageal cancer: oesophageal adenocarcinoma. Oesophageal adenocarcinoma, the incidence of which has risen 6-fold in the past few decades, is frequently associated with gastro-oesophageal reflux disease and its complications. Studies in the USA have shown that diagnosis only occurs in ~7% of people with the disease, and approximately half of all patients with this type of cancer die within a year of diagnosis, despite advancements in treatment.

"We are poised on the brink of having new techniques that should help us predict the risk of GI cancers in the future, ensure we prevent those we can, and detect many others far earlier than we do now."

Regular screening of patients with gastro-oesophageal reflux disease using non-invasive tissue sampling in primary care would allow for the determination and monitoring of cancer risk based on the presence/level of dysplasia observed, i.e. in relation to Barrett's disease – with high specificity, decreased sampling bias, and less discomfort for the patient. This is key as early detection, particularly in GI cancer, has a dramatic effect on prognosis. Prof Fitzgerald's model stratifies patients according to their level of risk, with the lowest levels being advised to make lifestyle changes, those at level 4 receiving secondary care endoscopy, and tertiary care provided for those at level 5. It is believed that this model could be applied population-wide in a cost-effective manner, and would allow increased early detection of oesophageal cancers.

In a UEG press release dated 27th October, Prof Fitzgerald said: "Our growing understanding of the cause of these cancers, coupled with new diagnostic techniques, mean we are in a good position to start developing precision prevention programmes. These would ensure we triage individuals based on their relative risk and apply the most appropriate screening, prevention, and treatment options to each individual."

Other GI cancers could soon be included within similar models to the one proposed by Prof Fitzgerald, as new methods of predicting the risk of, and identifying, various GI cancers are being evaluated. For example, a cluster of genetic mutations that, in association with other factors, are predictive of the risk of Lynch syndrome (hereditary non-polyposis colorectal cancer), have been identified using genetic analysis. "We are poised on the brink of having new techniques that should help us predict the risk of GI cancers in the future, ensure we prevent those we can, and detect many others far earlier than we do now," concluded Prof Fitzgerald.



Exhibiting companies

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4P Medicine and Its Relation to Colorectal Cancer

PROACTIVE medicine is on the rise, with a more modern approach to diagnosis and treatment becoming more frequent, according to a presentation at UEG Week 2015. Dr Antoni Castells, Gastroenterology Department, Hospital Clinic, Barcelona, Spain, described the change as a move away from traditional reactive medicine to a much more efficient process. The process involves four 'p's – predictive, preventative, personalised, and participatory medicine, with an aim of ensuring that diagnosis and treatment are both readily available and effective in preventing disease onset, and that they are specific to the patient; the process should also directly involve the patient. It is hoped that this idea will become universally prevalent in the future, and that it will catalyse faster and more effective treatment of patients.

One aspect of the personalised approach has arisen from the advent of human genome sequencing, specifically next-generation sequencing (NGS). NGS allows an analysis of genes and any differences that a patient or population harbour compared with the general population. This can be applied to colorectal cancers (CRCs), which come in a number of forms, as each form has a number of associated genes. Identification of these genes can define diagnosis and inform the treatment, prognosis, and family history of a patient. One area in which this technique will soon be used is the surgical decision process; mutations in certain areas of the *APC* gene responsible for familial adenomatous polyposis alter the severity and heritability of the condition and thus lead to a difference in the invasiveness of the surgery required.

Overall, the use of a 4P-directed risk stratification model may be beneficial for both patients and their families...

Current best practice for the screening of CRC is the use of colonoscopy, which is offered every 10 years to all those over 50 years of age in most European countries. However, no randomised controlled trials have been put in place to test this method and it is a large economic burden on

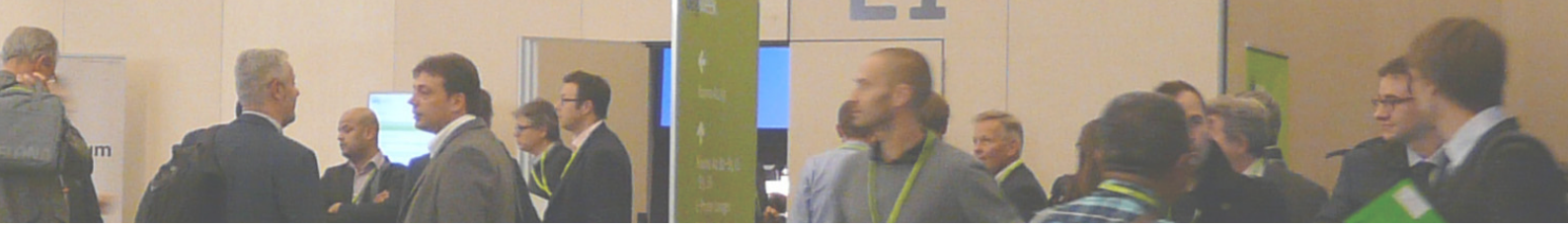
most healthcare systems, especially when considering that only 10.2% of people who are screened will require any further intervention. Colonoscopy is also associated with risk, with 2.4% of people consequently experiencing a serious gastrointestinal event.

Dr Castells suggested a risk stratification model, whereby people who are mostly likely to benefit from the procedure are selected for colonoscopy based on a number of factors. The first factor is individual characteristics such as sex, age, familial history, and smoking status, which are all risk factors for CRC. However, these factors alone are not enough to recommend a colonoscopy. A second factor that could be considered is genetic markers; currently 41 single-nucleotide polymorphisms (SNPs) that increase the risk of CRC onset have been identified. This number is believed to represent ~10% of the genetic susceptibility of the disease, and many more are expected to be found in the coming years. This would allow the use of NGS, which could provide a risk profile based on these SNPs and age; combining these two factors would give a better indication as to whether colonoscopy is required. In order to further avoid invasive testing, the final factor involves the identification of novel biomarkers in faecal matter, which can be collected easily and is tolerated better by patients than blood samples. The benefit of this is that it may contain exfoliated neoplasmic cells and blood that can be tested for genetic mutations. Using these methods would reduce discomfort and risk to patients as they may cause a reduction in the number of required colonoscopies.

Overall, the use of a 4P-directed risk stratification model may be beneficial for both patients and their families, especially with hereditary conditions such as some CRCs. Further research is required to better characterise the genetic, biological, and epidemiological factors used in this model.

Zonulin Associated with Non-Coeliac Gluten Sensitivity and IBS

HIGHER than normal blood levels of zonulin may lead to non-coeliac gluten sensitivity (NCGS) and irritable bowel syndrome (IBS), suggest results from a study presented at UEG Week 2015. Discovered in 2000, the protein has already been associated with coeliac disease due to its role in regulating the permeability of the intestine. In light of this new knowledge, the researchers who conducted the study hope that their research will enable the development of new therapies for autoimmune conditions.



"This study has increased our understanding of zonulin and how it might contribute to the development of these common and disabling bowel conditions."

Zonulin is found within intestinal cells and is the only known human protein that controls the size of gaps between these cells, orchestrating the passage of water, cells, and nutrients into and out of the intestine. Consequently known as a 'tight junction regulator', previous research has shown that the protein is produced and released by triggers including intestinal bacterial infections and gluten. The junctions between the intestinal cells that are usually tight remain open when zonulin is present, causing an excess of substances to be released from the bowel. This starts an inflammatory cascade in those with autoimmune conditions such as coeliac disease or Type 1 diabetes, which damages the intestinal wall.

In this study, the blood levels of zonulin were measured in 27 patients with NCGS, 15 with diarrhoea-predominant IBS (IBS-D), 15 with coeliac disease, and in 15 healthy volunteers. Patients with coeliac disease were discovered to have the highest zonulin levels (mean 0.033 ng/mg), although NCGS patients were a close second (mean 0.030 ng/mg), followed by those with IBS-D (mean 0.012 ng/mg). In comparison, the mean zonulin levels of healthy volunteers were a mere 0.007 ng/mg. "We were intrigued to find that blood levels of zonulin were almost as high in patients with NCGS as in those with coeliac disease," said Prof Giovanni Barbara, Associate Professor, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy, in a UEG press release dated 28th October. Of note, blood levels of zonulin dropped considerably in NCGS patients when they were on a gluten-free diet.

"This study has increased our understanding of zonulin and how it might contribute to the development of these common and disabling bowel conditions," Prof Barbara concluded. "Hopefully, our work will lead to new diagnostic and therapeutic strategies for patients with these and possibly other autoimmune conditions."

New Capsule for Faecal Microbiota Transplantation

TREATMENT of *Clostridium difficile* infection and other bowel conditions using a new oral capsule form of faecal microbiota transplantation (FMT) is safe and effective, according to new research presented at UEG Week 2015. The researchers noted that the change from traditional methods to an oral formulation simplifies the administration of the treatment, and hope that it will consequently start to take over as the standard therapy for the condition.

Infection with *C. difficile* causes cell death, intestinal inflammation, and severe diarrhoea. Spread through the ingestion of spores, the infection can last for several weeks or even months, and current therapy often does not completely eradicate the symptoms: around one-third of patients will experience a recurrent infection and, of these, many will experience multiple recurrences. As shown by the chronic illness and continual hospitalisations caused by the infection perennially returning, the consequences of this can be severe.

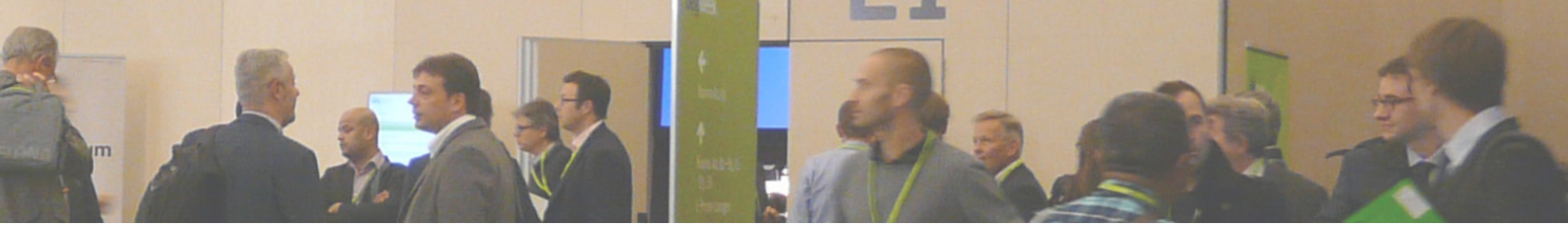
FMT is traditionally performed using a nasogastric tube, endoscopy, enema, or colonoscopy to transplant a liquid faecal suspension from a healthy donor into an infected patient. Prof Antonio Gasbarrini, Professor of Gastroenterology, Department of Internal Medicine, A. Gemelli University Hospital, Rome, Italy, highlighted the drawbacks of this method in a UEG press release dated 6th October: "FMT is an excellent treatment for *C. difficile* infection, but traditional methods are time-consuming and technically challenging," he stated. The new method, using capsules containing a frozen suspension of faecal material from healthy donors, has been shown to be both safe and more effective. "Advances in the preparation and delivery of FMT will lead to its wider acceptance as a safe and effective treatment for *C. difficile* infection that could supersede antibiotics," Prof Gasbarrini added.

Twenty patients with *C. difficile* infection took part in the FMT capsule study. Each patient had either failed to respond to antibiotic medications or had been hospitalised at least twice as a consequence of the symptoms they experienced. The capsules were administered to the patients on 2 consecutive days, with the initial results showing that symptoms were resolved after the first 2 days of treatment in 14 of the 20 patients (70%), who subsequently experienced no further symptoms for 8 weeks. Four of the remaining patients became symptom-free after a second course of treatment, meaning that there was a 90% resolution rate.

Prof Gasbarrini and his team are particularly encouraged by these results given that the capsule treatment resolves the drawbacks of the traditional methods. "Although larger studies are needed to confirm these findings, this study could certainly lead to more widespread use of FMT in the treatment of recurrent *C. difficile* infection," he concluded.

Innovation in Gut Microbiome Sampling

SAMPLING and characterisation of gut microbiota to aid research into a range of gastrointestinal diseases and related cancers has received a boost following the launch of a new diagnostic kit from Origin Sciences Ltd.



The gut microbiome has traditionally been studied via stool samples, but the Oricol™ Microbiome Research Kit allows samples to be collected directly from the rectal mucosa. The new kit was announced at UEG Week 2015 and described in a press release dated 26th October.

Gut microbiome research is a fast-growing area within life sciences as researchers strive to understand the interactions between bacterial populations in the gut and a range of gastrointestinal and nutritional diseases and cancers, as well as the relationships between gut microbiomes of various human populations. Nascent studies have also suggested a relationship between the gut microbiome and common allergies and allergy-related diseases. While traditional methods of sample collection have proven useful, it has been shown that increased bacterial diversity and an enrichment of phyla associated with the mucosa can be obtained using the new kit. Utilisation of the new sampling method may lead to a more representative model of the gut microbiome and allow for the study of more complex interactions between the different bacterial species and between host cells. The greater reproducibility of sample collection and reduction in processing should hopefully lead to an improvement in the quality of experimental data.

From a clinical point of view, the new research kit may also assist in the diagnosis of, or review of prescribed treatments for, gastrointestinal diseases such as inflammatory bowel disease. The kit represents a relatively quick and easy method of sample collection that requires no bowel preparation, which should increase the convenience of testing. Studies have shown that patients prefer the new method compared with the traditional, more invasive methods of mucosal sampling, which is reflected in high levels of acceptability and compliance.

The recently appointed CEO of Origin Sciences, Mr Paul Weinberger, said: "The microbiome is a growing area of research interest for the life sciences and pharmaceutical industries and has seen significant investment. However, it is a particularly challenging area to work in, and new techniques and tools are required."

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The Future of Hepatological Research

MUCH progress has been made in the field of hepatology in 2015, with large steps being taken towards improved treatments. Prof Heiner Wedemeyer, Research Group Leader, Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany, covered a selection of topics at UEG Week 2015, including hepatitis, autoimmune conditions, primary biliary cirrhosis, hypertension, and alcoholic hepatitis.

New research published in February looked at the connection between different autoimmune diseases using genome-wide association study data and epigenetic data. The results showed that 69% of the identified disease loci were shared by more than one disease, although no two diseases shared more than 38%. This does, however, raise important questions for potential novel therapeutics in Crohn's disease, coeliac disease, primary biliary cirrhosis, and primary sclerosing cholangitis.

Recent research in patients with primary biliary cirrhosis has suggested that many carry the disease prior to cirrhosis development, while some never reach that stage; for this reason it has been suggested that the correct term for the disease should be primary biliary cholangitis (PBC).

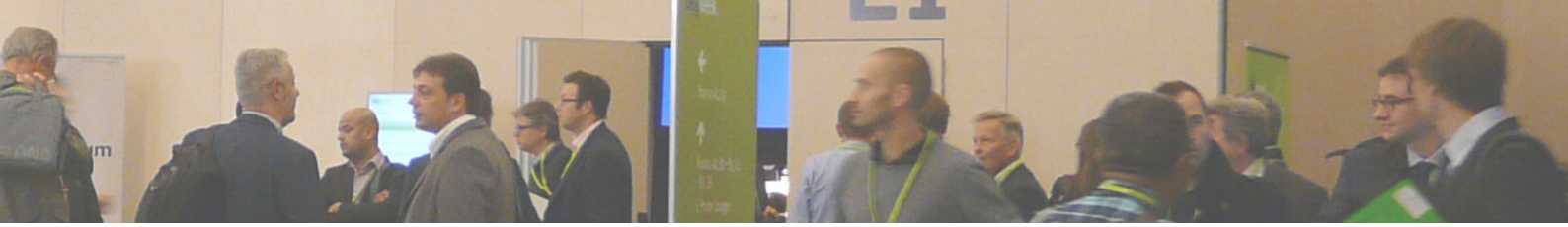
Participants

13,203

A recent randomised controlled trial (RCT) tested the efficacy and safety profile of obeticholic acid (OCA). A total of 165 patients with PBC were randomised to varying doses of OCA or placebo alongside their current treatment method. OCA exhibited a superior effect on the study endpoint compared with placebo, with 69% of patients experiencing a ≥20% reduction in alkaline phosphatase levels compared with only 8% of those taking placebo. The authors noted that in all doses there was a reduction, although the lowest incidence of pruritis was observed at 10 mg (the lowest dose).

Prof Wedemeyer noted that alcoholic hepatitis is becoming a much larger issue across Europe, particularly in the UK. A large RCT screened 5,000 patients and went on to randomise 1,103 of them to prednisolone or pentoxifylline with a placebo, or both. The results suggested that pentoxifylline did not improve survival in patients at 28 days, while prednisolone was associated with a non-significant reduction in 28-day mortality. "What is definitely out is pentoxifylline; it should no longer be used. It may only cause side effects and do not use it in your clinical practice," Prof Wedemeyer concluded.

There have been many developments in the treatment of viral hepatitis C (HCV), and a number of new agents have been brought to clinical trials. The new agents fit into one of three categories: polymerase inhibitors,



protease inhibitors, and NS5A inhibitors. This allows a new set of treatment combinations that may be used. These drugs have been shown to have almost no side effects and response rates of 90–100%. Life expectancy in patients with chronic HCV and liver fibrosis is as high as the general population if a sustained virological response is achieved, according to the results of a trial published in November 2014. The data included 530 patients followed over 10 years; the survival rate was 91.1%.

In the past there has been a large amount of debate regarding the potential hepatotoxicity associated with statins. While a large amount of evidence has been published on each side of the argument (positively suggesting a hepatotoxic effect of statins or the reverse) in both murine and human models, there are many upcoming studies which suggest that statins are safe. Furthermore, recent data have suggested that the use of statins may decrease the risk of oesophageal adenocarcinoma.

"What is definitely out is pentoxifylline; it should no longer be used. It may only cause side effects and do not use it in your clinical practice."

A Look into the Future of Endoscopy

RAPID developments in endoscopy have contributed to steady improvements in the detection and care of gastroenterological diseases, which have subsequently led to improved patient outcomes. In light of these developments, Prof Peter Siersama, Department of Gastroenterology & Hepatology, University Medical Center Utrecht, Utrecht, Netherlands, was invited to speak on recent advancements in endoscopy at UEG Week 2015.

Despite all the benefits associated with endoscopy, it remains a relatively expensive procedure. Many patients undergo endoscopy as part of a screening process for cancers or monitoring of other conditions, and it has been suggested that there is a need for highly sensitive, low-cost alternatives. Prof Siersma began his talk by describing a highly specific new technology, the Cytosponge™, that may help to reduce the need for expensive endoscopy procedures in patients with Barrett's oesophagus. The Cytosponge is a tablet attached to a string that can be swallowed by the patient. The tablet dissolves within the oesophagus to reveal a brush that unfurls and collects cell samples from each region of the oesophagus. The cells are then subsequently stained for trefoil factor 3 in order to detect dysplasias. The device has performed well in trials carried out in

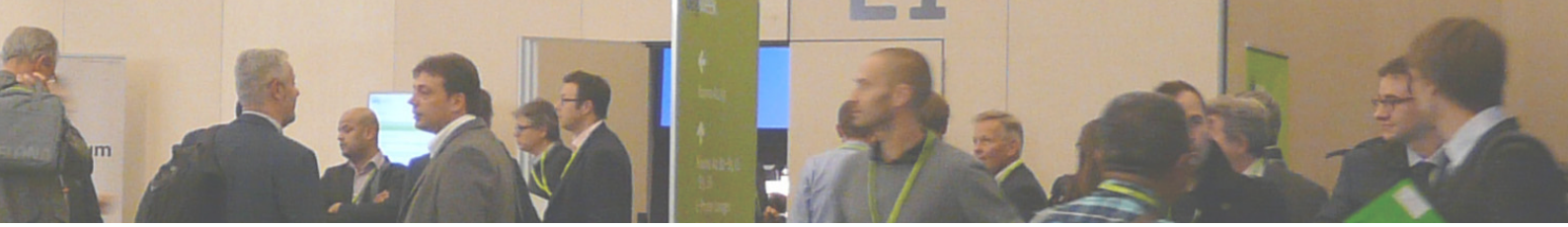
UK hospitals and including more than 1,000 participants (463 control patients with dyspepsia and reflux symptoms and 647 patients with Barrett's oesophagus). Prof Siersama commented: "I think that the take home message here is that it is indeed very simple and inexpensive, which is what makes it so interesting, but we need more studies before we know if this is a test which can be used to screen for patients with Barrett's oesophagus."

Prof Siersama also discussed findings published earlier this year that compared the risk of gastrointestinal (GI) bleeding associated with warfarin with that associated with two novel anticoagulants, rivaroxaban and dabigatran. These drugs are often used for the prevention of stroke and embolism, but they are also associated with a low risk of intracerebral haemorrhage and an increased risk of GI bleeding. A retrospective study compared the use of dabigatran, rivaroxaban, and warfarin over a period of 3 years in patients with and without atrial fibrillation. Over 60,000 patients administered rivaroxaban were compared with more than 8,000 patients administered dabigatran and more than 67,000 patients given warfarin, or as Prof Siersama highlighted: "an ideal group to do calculations for complications." The study concluded that, overall, there was no difference in the risk of developing a GI bleed between the novel anticoagulants and warfarin. When the patients were stratified according to age, however, a higher risk of bleeding was evident in patients over 65 years of age who received a novel anticoagulant. As a result of this analysis it has been suggested that care should be taken when prescribing these novel drugs to older patients.

Top attending country

United Kingdom

There is an increasing focus on the detection of adenomas by endoscopy, particularly colonoscopy, and therefore it is unsurprising that Prof Siersama decided to also address this topic. He highlighted the need to reduce the chance of missing adenomas, a problem associated with interval colorectal cancer, with increased training suggested to be among the most immediate methods of achieving this aim: "There is another topic that is important, and that is training. If we train people then maybe the adenoma detection rate (ADR) can be improved." Prof Siersama also



drew special attention to a study that highlighted the improved quality of endoscopy that can be achieved by training leaders in endoscopy units. It was found that, not only did the ADR of the leaders improve, but so did those of the other endoscopists in participating units (average ADR increase of 3.9%). Prof Siersama also discussed the use of chromoendoscopy in patients with a suspected adenoma. While many expert centres have suggested that a higher rate of dysplasia detection can be achieved with chromoendoscopy, findings from Prof Siersama's own clinical centre suggest that chromoendoscopy does not significantly increase the rate of dysplasia detection compared with white light endoscopy when considering random or targeted biopsies. Therefore, it was suggested that chromoendoscopy should be used selectively, e.g. in patients at higher risk such as those presenting with primary sclerosis cholangitis or a stricture.

In conclusion, endoscopy remains an important tool for the detection and monitoring of tumours and other diseases of the GI tract, despite the continual challenge of funding.

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Inflammatory Bowel Disease Research in 2015

DEVELOPMENTS in inflammatory bowel disease (IBD) research were summarised by Prof Laurence Egan, Department of Pharmacology, Clinical Sciences Institute, National University of Ireland Galway, Galway, Ireland, at UEG Week 2015. Prof Egan gave a comprehensive presentation that ranged from the aetiology and pathogenesis of the disease to information on new ways to manage and treat IBD patients, highlighting progress that has been made during 2015.

Beginning his presentation with the possible role of dietary emulsifiers in the aetiology of IBD, Prof Egan reported on a study demonstrating that ingestion of the emulsifiers carboxymethylcellulose

and polysorbate 80 narrows the thickness of the mucus layer in mice, allowing a closer association of microbes with the epithelial tissue. This narrowing of the mucus layer leads to a greater susceptibility to the development of ulcerative colitis (UC) in predisposed individuals. More research is required to confirm whether this mechanism is relevant in humans.

Prof Egan also described the usefulness of ultrasound for monitoring inflammatory activity in patients with Crohn's disease. In a study of 49 patients, clinical and endoscopic characterisation showed normal C-reactive protein (CRP) levels in many patients, with even those displaying higher CRP levels shown to have achieved remission or to have a mild form of the disease. Following ultrasound investigation, however, the physicians opted to change the patients' management plan in 60% of cases in favour of more aggressive therapy or even referral for surgery. Commenting on the results, Prof Egan stated: "Ultrasound has the potential to improve disease control by providing appointive care and objective assessment of information in a non-invasive and extremely safe way, and lead to better decisions."

Rounding off his presentation with a description of novel therapies, Prof Egan described a placebo-controlled randomised trial of UC patients, 38 of whom received faecal microbiota transplantation (FMT) from healthy donors and another 37 who received placebo. Following administration of FMT alongside regular therapy for 6 weeks, remission was achieved in 2 (5%) placebo patients compared with 9 (24%) FMT patients at 7 weeks. As FMT induced remission in a significantly greater percentage of patients with active UC than placebo, and with no difference in adverse events, this treatment was shown to hold some promise in UC patients.

"In 2015, have we learned the cause of IBD? Certainly not. Have we got a cure for IBD? Certainly not either, but we have made scientific, clinically significant, incremental advances in IBD and, importantly, we have learned how to frame new research questions for future IBD research," Prof Egan concluded.

Carcinogenic Risks of Red and Processed Meats

A PRESS RELEASE published during UEG Week 2015 discussed the International Agency for Research on Cancer's (IARC) recent evaluation of the carcinogenicity of red meat and processed meat, and has gained considerable attention. An international advisory committee that met in 2014 recommended red meat and processed meat as high priorities for evaluation by the World Health Organization's IARC Monographs Programme, as several epidemiological studies have indicated that high consumption of these products increases the risk of developing several different types of cancers.

Recent estimates by the Global Burden of Disease Project suggest that around 34,000 cancer deaths per year are attributable to diets high in processed meat...

It is not yet fully understood how an individual's risk of developing certain types of cancer is increased by consuming red or processed meat.

However, the carcinogenic nature of meat is attributed to chemicals that form during processing or cooking, such as the N-nitroso compounds and polycyclic aromatic hydrocarbons (PAH) which form during meat processing, for example. Cooking red or processed meat may also produce PAH in addition to heterocyclic aromatic amines and other potentially harmful chemicals that are also found in other foods and in air pollution. While the risks are thought to be small, they remain important for public health as many people worldwide eat meat, and meat consumption is increasing in lower and middle-income countries.

Recent estimates by the Global Burden of Disease Project suggest that around 34,000 cancer deaths per year are attributable to diets high in processed meat, and that 50,000 could be a result of red meat consumption.

IARC's evaluation, which involved a thorough review of existing scientific literature, has classified red meat consumption as 'probably carcinogenic to humans' (Group 2A), using 'limited evidence' from epidemiological studies showing positive associations between the consumption of red meat and cancer in exposed humans and strong mechanistic evidence supporting a carcinogenic effect. This association was observed mainly for colorectal cancer (CRC), but associations were also found for pancreatic and prostate cancer. Processed meat has been classified as 'carcinogenic to humans' (Group 1), based on 'sufficient evidence' from epidemiological studies of a causal link between CRC and the consumption of processed meat in humans. An association with stomach cancer was also seen, although the evidence is not conclusive. The study further suggests that the risk of developing cancer increases with the amount of meat consumed: an analysis of 10 studies estimated that the risk of CRC increases by 18% for every 50 g portion of processed meat consumed daily. The cancer risk associated with consumption of red meat is more difficult to estimate, but if the association were to be proven to be causal then the data from the same studies suggest that the risk of CRC may increase by 17% for every 100 g portion of red meat consumed daily.

IARC's review does not instruct people to stop eating red or processed meats, but it does suggest that reducing consumption of these products can reduce the risk of CRC, supporting the

recommendations of previous reports such as WHO's 'Diet, nutrition and the prevention of chronic diseases' published in 2002. However, the existing evidence does not yet permit a conclusion about whether a safe level exists. Early next year, WHO plans to address the public health implications of the latest research and establish the place of processed meat and red meat within the context of a healthy diet.

Call for Action to Combat Pancreatic Cancer

GREATER action from healthcare providers and governments, along with the introduction of new public health initiatives, have been urged by UEG to raise awareness of pancreatic cancer. In recognition of World Pancreatic Cancer Day, which occurred on 13th November this year, this initiative will span from increasing our knowledge on risk factors and symptoms, to improving early diagnosis, treatment, and survival rates of the disease.

Despite being the eighth most common cancer in Europe, little is known about pancreatic cancer, and survival rates remain at a mere 3–6%. It is particularly hard to detect, as symptoms usually do not manifest until a later stage of the disease, and the condition is also challenging to treat. "Pancreatic cancer is a deadly disease with highly unmet medical need. It is vital that there is more awareness of the risk factors and symptoms of pancreatic cancer among the public and medical community to allow more people to be diagnosed in time for surgery – currently the only potential for a cure," explained Prof Matthias Löhr, Professor of Gastroenterology and Hepatology, Karolinska Institutet, Stockholm, Sweden, in a UEG press release dated 10th November.

According to UEG, the responsibility of instigating change with regard to established risk factors for pancreatic cancer (including chronic pancreatitis and diabetes, etc.), and of raising awareness of common symptoms such as abdominal or back pain, jaundice, and weight loss, to help with early diagnosis lies predominantly with public influencers. Recent research has also demonstrated a strong link between pancreatic cancer and common bacterial infections. The stomach bacterium *Helicobacter pylori*, for example, may contribute to the progression of the disease by acting in conjunction with other risk factors to impact upon inflammation and immune response. It is clear that further research is required in order to learn more about the cancer and improve patient outcomes in the coming years.

"As well as action from healthcare providers, increasing public awareness of the symptoms of pancreatic cancer and following some simple lifestyle improvements will go a long way to ensuring that pancreatic cancer survival rates dramatically improve within the next few years," Prof Löhr concluded.

Najib Haboubi

Professor of Health Sciences, Liver and Gastrointestinal Pathology, and Consultant Histopathologist, Department of Pathology, University Hospital of South Manchester; University of Salford Manchester, Manchester; Liverpool John Moores University, Liverpool, UK.

Q: What motivated you to begin a career in medicine and why did you decide to specialise in gastroenterology?

A: Like many doctors, I come from a medical family and so I suppose you might say I got to 'feel' medicine before I understood what it really was; the satisfaction from it became etched into my bones and the decision was made for me. As to why I chose pathology and then gastroenterology as a specialty, a combination of intellectual curiosity and an equal thirst for both research and practice is the answer for both.

Q: Having trained in both Iraq and the UK, what significant differences in terms of medical training have you observed between these two countries?

A: I was trained in Iraq during the 'golden period'. We were very well educated, having been exposed to practical as well as theoretical elements, and we followed a hybrid of the USA and UK systems. However, I found the British training system to be a complete one and probably the best in the world. The trainees in the UK have to go through vigorous training and scrutiny for at least 5 years before they become eligible to sit the final exam, and if they pass they are almost equipped to be consultants. By and large, the training in the UK is controlled by the college and supervised by postgraduate deaneries, which ensures, more or less, training uniformity throughout the nation. The training centres in Iraq varied widely.

Q: A recent article that you co-authored describes the challenges in the differential diagnosis of inflammatory bowel disease (IBD) and other colitides – can you speculate on how these difficulties may be resolved in the future?

A: This was the last in the series of articles that I have written and co-authored during the previous 30 years that aim to outline the difficulties in diagnosing IBD from mucosal biopsies. These articles also provided a system that stabilises the variability of subjectivities present when pathologists make such diagnoses. The core message we are suggesting is that making a diagnosis and further sub-categorisation of IBD, and furthermore to distinguish IBD from its mimics, is the combined responsibility of the pathologist and the clinician. We also suggest that the final diagnosis is best achieved in a clinico-pathological meeting designated for non-malignant gastrointestinal cases, when all relevant information becomes available and the pathologist can interpret the changes with a full view of the clinical and endoscopic findings.

Q: What is your opinion on the feasibility of introducing screening programmes for colorectal cancer in the general population?

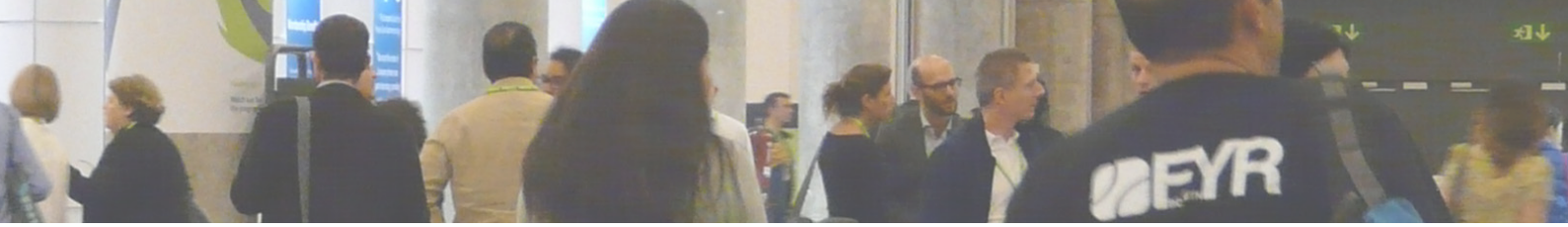
A: Screening is feasible, of course, but pragmatic decisions need to be made in order to create uniformity. The tests range from simple, low-cost breath tests to much more invasive and expensive full colonoscopies. Factors such as, for example, the age of individuals to be screened, funding, accuracy of the tests, and patient acceptance and compliance need to be addressed when deciding on an appropriate programme model.

Q: What do you consider to be the most significant developments in the field of gastroenterology since you began your career?

A: Although many significant developments have been made, I would suggest that the discovery of *Helicobacter pylori* and the introduction of hepatitis vaccinations top the list.

Q: What areas of gastroenterology do you feel are the most under-researched or underfunded, and would benefit most from more resources?

A: In my opinion, neurogastroenterology and radiation bowel disease.



Q: In your opinion, what are the greatest challenges currently facing the field of gastroenterology?

A: Similar to any field, medical or otherwise, excellence comes through hard work, dedication, and diligence. The trainees' hunger for excellence, both in research and service, will be critical if we are to advance. This is just as true for gastroenterology as it is for any other field.

Q: Please tell us a little about your work with the Association of Coloproctology of Great Britain and Ireland (ACPGBI); what are the aims of this group?

A: I was a founding member of the ACPGBI and I have served on the council for 21 years. I was elected president in 2009/2010; I was the first non-surgeon to have that honour. Our aims are to: build training programmes, supervise and improve training, and promote research and good clinical practice within the field of coloproctology.

Q: What achievement in your medical career are you most proud of?

A: Being elected as president of the ACPGBI and receiving various honorary memberships of national bodies and professorships across the UK and abroad.

Q: How important do you think congresses such as UEG Week are for gastroenterologists?

A: Any forum where the best experts in the various fields of gastroenterology can meet, talk, teach, and share is invaluable. UEG Week is the best congress in the world as it brings together a huge amount of expertise in luminal and extra-luminal gastroenterology under one large roof for all of us to learn and share experiences.

Matt Rutter

Professor of Gastroenterology, Durham University, Durham; Consultant Gastroenterologist, University Hospital of North Tees; Clinical Director, Tees Bowel Cancer Screening Centre, Stockton-on-Tees, UK.

Q: Where did you begin your medical career and what drove your decision to specialise in gastroenterology?

A: I am the first medic in my family. I was inspired by the father of a school friend, who was an eminent gastrointestinal (GI) surgeon. I trained in Newcastle and it was during my rotation as senior house officer that I fell in love with gastroenterology – I was fascinated by the wide range of diseases, being able to turn a sick patient's life around with accurate diagnosis and effective treatment, and of course endoscopy.

Q: How has the field of gastroenterology evolved since you began your career? Have there been any changes or advancements that you feel have made a particularly significant impact?

A: It has changed tremendously. Upper GI disease has been transformed by the discovery of *Helicobacter* and by proton-pump inhibitor therapy. Advances in diagnostics, particularly endoscopy and cross-sectional imaging, have led to faster diagnosis and earlier treatment opportunities. Endoscopy in particular has evolved from being something of interest to a few enthusiasts to a subspecialty in its own right – it continues to develop at an incredible rate, with high quality diagnostics, screening, and the ability to prevent cancer by the endoscopic resection of precancerous polyps. Therapeutic endoscopy is ever encroaching on previous surgical territory. Disease genetics and the use of large datasets are areas that have also rapidly expanded – we will hear more and more about these in the coming years.

Q: What does your work as the Chair of the European Society of Gastrointestinal Endoscopy (ESGE) Quality Improvement in Endoscopy Committee entail? What are the aims of this group, and have there been any notable successes or challenges?

A: The ESGE Quality Improvement Committee was instigated in 2013. Its aims are: to improve the global quality of endoscopy and the delivery of patient-centred endoscopy services; to promote a unifying theme of quality of endoscopy within ESGE activities, achieved by collaborating with other

ESGE committees and working groups, and underpinned by a clear quality improvement framework; and to assist all endoscopy units and endoscopists in achieving these standards.

An initial key objective has been to help improve the quality of GI endoscopy by producing a framework of performance measures for endoscopy, including quality of independent endoscopists and quality of endoscopy services (covering all aspects of the service including equipment, decontamination, waiting times, and patient experience), by developing robust, evidence-based performance measures. The aim of this was to set a minimum standard for individual endoscopists and for the endoscopy service, and to permit endoscopy units to measure their services against this patient-centred framework. ESGE, in conjunction with United European Gastroenterology (UEG), created four working groups for the GI tract – upper GI, lower GI, pancreatobiliary, and small bowel. A fifth 'Endoscopy Service' working group was also created. Almost 100 people from over 30 nations are involved in the process – a major challenge in coordination! Output from the project is due for publication in 2016.

Q: Diseases such as inflammatory bowel disease (IBD) and coeliac disease are becoming better known to the general public. Do you feel that these diseases are truly becoming more prevalent or is greater awareness leading to increased diagnosis? Is there anything more that can be done to reduce the prevalence of these conditions?

A: Although there are a few exceptions, I think that most of the increased prevalence is due to greater public awareness, improvements in diagnostic tests, and better access to these tests with lower thresholds for investigation.

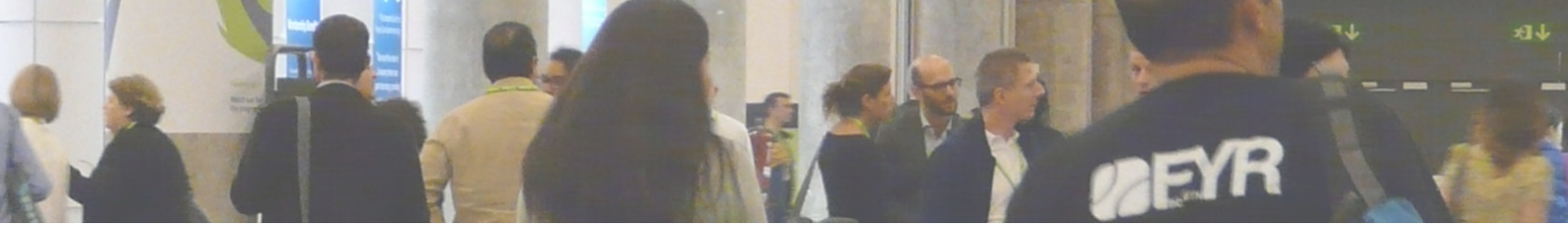
Q: What is your opinion on the introduction of large-scale public screening programmes for colorectal cancer (CRC), especially with regard to issues of compliance, diagnostic performance, and the possibility of overtreatment?

A: CRC screening has major advantages compared with many screening programmes – in particular a clearly defined and easily treatable premalignant stage (the precancerous polyp). Although colonoscopy is the best screening test on an individual level, no country can afford primary colonoscopy screening for all of its population. Near-patient testing, particularly with faecal immunochemical testing, allows true population screening, which will benefit more people. Although current stool tests are relatively non-specific, this will improve over time, increasing the potential of this form of screening. Nevertheless, this form of screening primarily works by down-staging cancer rather than reducing cancer incidence (preventing cancer). True population-wide, flexible sigmoidoscopy screening is being rolled out in the UK, and the evidence is compelling that this reduces CRC incidence as well as mortality.

The issue of overdiagnosis and overtreatment is important, but perhaps is less of a problem with CRC screening than with most other screening programmes. Undoubtedly, not all people with a faecal occult blood positive result will have cancer, yet all will undergo a colonoscopy. Thankfully, modern colonoscopy is a very safe procedure, and one-third to one-half of people will have precancerous polyps. Of course, not all of these polyps would progress to cancer so there is overtreatment of polyps, but polypectomy is relatively and increasingly safe, and there is compelling evidence that polypectomy prevents CRC. Neither of these two overtreatments place a significant burden on patients. Finally, not all CRCs would cause patients harm during their lifetime. This may be particularly true for polyp cancers. Thankfully, nowadays many of these patients have their cancer removed endoscopically and avoid surgery altogether. Evidence from the FlexiScope trial demonstrates that patients with distal CRC present within 4 years of CRC development – a lead time that is short enough to indicate that asymptomatic detection will benefit the vast majority of screening patients during their lifetime.

Q: What do you feel are the greatest challenges currently facing the field of gastroenterology?

A: There are, of course, many. Alcohol-related GI disease is becoming increasingly prevalent and



challenging. Improving the quality of everyday endoscopy is a particular passion of mine – challenging, but the rewards in terms of patient health are very large, given the tens of millions of endoscopic procedures that are performed in Europe every year. Equality of access to healthcare remains a great challenge, although this is not specific for gastroenterology.

Regarding research, I think that interpreting the genetics of conditions such as IBD (both the underlying causes of IBD and the biology of disease progression and prognosis) and translating this into clinically useful information with the potential for individualising treatment regimens is an exciting challenge, although I think there is still a long way to go.

Q: Are there any areas of gastroenterology research that you would like to become more involved with in the future?

A: I am passionate about striving to improve the quality of endoscopic procedures. I see a great opportunity in pooling endoscopy data from different centres for large-scale research and evaluation. To this end, I chair the UK National Endoscopy Database project, which aims to pool all endoscopy data at a national level. In endoscopy, I am fascinated to see how robotics will integrate with current endoscope technology. Finally, my interest in IBD research, particularly surrounding cancer risk, remains very strong.

Q: How important are congresses such as UEG Week to consultants such as yourself?

A: UEG Week has developed into a vital conference for both clinical and academic gastroenterologists – for education, for research, for reflection, and perhaps above all, for networking – many lasting international collaborations and friendships have arisen over coffee at UEG Week.

Q: What do you feel has been the most fulfilling part of your medical career thus far?

A: I would pick three things. Firstly, the joy of managing patients with IBD – it is a long-term relationship and tremendously rewarding. Secondly, the rapid evolution of diagnostic and therapeutic endoscopy into high-quality, patient-centred, surgery-preventing procedures. Thirdly, the strong international gastroenterology community, which has enabled collaborative research and long-lasting personal friendships.

Q: Do you have any advice for medical students and junior physicians who are interested in specialising in gastroenterology?

A: Go for it! Gastroenterology is a fascinating, varied, practical, and rewarding specialty – we can make a real difference to people's lives. The gastroenterology community is also a very warm and welcoming family.

Joshua Melson

Assistant Professor of Medicine, Division of Digestive Diseases; Co-Director, Rush University Inherited Susceptibility to Cancer (RISC) Clinic, Rush University Medical Center, Chicago, Illinois, USA.

Q: What were the main reasons behind your decision to specialise in gastroenterology?

A: I was drawn to the field of gastroenterology due to the diversity of conditions we encounter, such as cancers, inflammatory bowel disease, and infections. I also thought colorectal cancer (CRC) screening by colonoscopy was unique in that it was a way to prevent a highly morbid and common cancer with a procedure.

Q: In your opinion, what more could healthcare providers do to ensure that more people participate in CRC screening programmes? How much of an issue is this in the USA at the moment?

A: According to a recent report from the Centers for Disease Control, about 62% of eligible Americans participate in CRC screening. Health systems need to track and identify patients who fail initial attempts at screening and then offer alternative approaches. This might be through the use of

'navigators' to improve compliance, or even offering an alternative method of screening from the one that failed to be successful previously.

Q: In a recent article that you co-authored ('Radiographic staging practices of newly diagnosed colorectal cancer vary according to medical specialty'), you concluded that gastroenterologists were less likely to include chest computed tomography (CT) in the initial staging of CRC despite current guideline recommendations to do so, and that educational efforts to improve compliance and standardisation may therefore be needed. Do you have any ideas on how this information can be disseminated to fellow gastroenterologists?

A: Good question. Firstly, providers should be made aware if they are ordering cross-sectional imaging and their own surgeons or oncologists, to whom they refer, then order additional staging examinations; this is a waste of resources that seems correctable. Perhaps if providers are aware that they are subjecting patients to multiple scans and trips to the hospital due to their inadequate staging practices then they will want to change. The impetus to study how CRC is radiographically staged in clinical practice came to me when I saw a patient who was informed previously by their gastroenterologist that their staging scans showed no metastatic disease. However, the prior staging was incomplete and had omitted a chest CT. Subsequent chest CT did show metastases and this was devastating to the patient who had initially been told that there was no metastases.

Q: How far has gastroenterology evolved since you began working in this specialty?

A: I finished my fellowship in 2009 and so it has not been that long since I came out of training. I run a high-risk clinic for genetic predisposition to gastrointestinal (GI) cancers at my institution. The biggest change since I started practising has been the availability and ease with which genetic predispositions can now be tested for. Sequencing of genes by next generation sequencing technology has led to an exponential drop in the cost of testing for deleterious mutations that predispose to GI cancers. This has led to the opportunity to assess for genetic predispositions clinically, which we would not have done in the past.

Q: Are there any demographic groups especially at risk of developing Barrett's oesophagus, and are there any lifestyle factors that contribute to the onset of the condition?

A: Factors predisposing to Barrett's oesophagus are duration of reflux, hiatal hernia, gastro-oesophageal reflux disease, and being male. There are data showing that smoking and diets that are low in fruits and vegetables are associated with cancer and development of high-grade dysplasia in patients that actually have Barrett's oesophagus.

Q: To what extent have treatment options improved for patients with Barrett's oesophagus in recent years? Are there any prominent unmet needs?

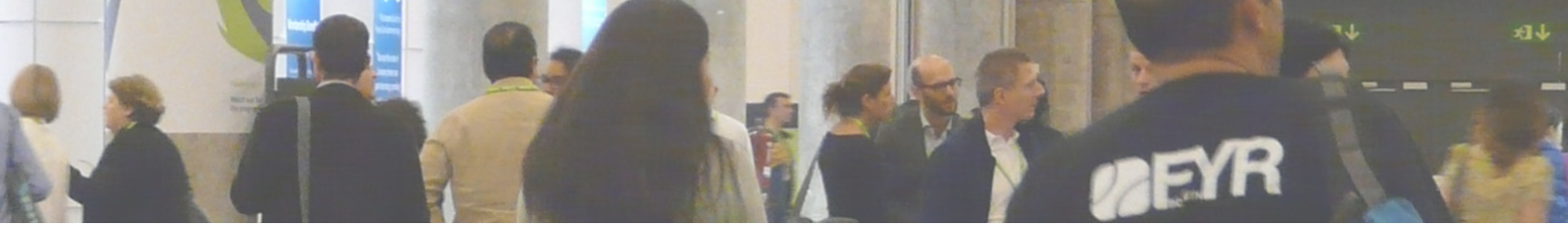
A: Ablative modalities, in particular radiofrequency ablation, have become an accepted standard approach for patients with high-grade dysplasia and now also for those with low-grade dysplasia. That being said, most patients with low-grade dysplasia and the vast majority of patients without any dysplasia will not progress along the dysplasia-to-carcinoma sequence, and it would be very useful to know which patients are at higher risk of progression. There has been, and there is, a lot of work on biomarkers in Barrett's – not just for predisposition to Barrett's oesophagus, but also for progression of dysplasia amongst those with Barrett's.

Q: How do you rate the current standard of healthcare provision in the USA?

A: Initiatives to track quality in recent metrics have meant that practices first need to monitor what they are actually doing in terms of metrics, such as surveillance colonoscopy intervals or adenoma detection rates. In general, these are a driver for GI practices to critically assess their practice patterns, in the hope of making them more efficient.

Q: What do you find to be the most fulfilling aspect of your work, and why?

A: I work with patients with high-risk predisposition syndromes for GI cancer conditions, like familial adenomatous polyposis and Lynch syndrome.



Understandably, patients are usually scared when diagnosed and concerned that their genetic conditions may lead to cancer and possibly death. The most satisfying thing for me is to have them realise that, with proper surveillance, they will most likely do well in spite of their genetic predispositions.

Q: What advice would you give to young gastroenterologists just starting out in their medical careers?

A: I tell our GI fellows that they are now finally at the time when they need to start thinking for themselves about what they really want to learn well. The USA medical training practice is very, very long and trainees get into a mentality of always being told what to do, what to learn, and what to study. However, GI fellowship is usually the last stop in their training, and trainees should critically assess what type of practice they want to have when they finish training. I tell them to look at their skills critically and to develop their training so that it is unique with some specialisation, in order to bring unique skills to a potential practice that they want to join.

Roberto De Giorgio

Associate Professor of Internal Medicine, Department of Medical and Surgical Sciences/ Digestive System, University of Bologna, St. Orsola-Malpighi Hospital, Bologna, Italy.

We were honoured to talk to the eminent Prof Roberto De Giorgio, an expert in internal medicine and gastrointestinal (GI) disorders, about his work, research, the medical societies he is involved in, as well as his overall opinion on the current state of the field of gastroenterology.

We began by discussing the enormous amount of change that he has observed in the field of gastroenterology following his graduation from the University of Bologna in 1985, an institution he works at today. First on the list for Prof De Giorgio is the advent of the proton-pump inhibitor. This treatment, "which has significantly reduced gastric acid secretion, just came out at that time," he explains. Prof De Giorgio then describes other vital developments, including the discovery of the pathogenetic role of *Helicobacter pylori*, the development of targeted treatments (referred to as 'biologicals') for inflammatory bowel disorders such as Crohn's disease and ulcerative colitis, and interferon and ribavirin treatments (and many more in recent times) for the hepatitis C virus. "I would also mention the technological advancement of endoscopy. We have now a very important technical instrument which is able to give very important clinical support to our diagnosis and even treatment for some GI diseases," he adds. "Last but not least, I would like to mention my own field with some advancement in GI motility, particularly with the recent acquisition of high-resolution manometry and the smart pill."

This moves us nicely onto Prof De Giorgio's own research interests. "My field is exactly in GI disorders, namely conditions characterised by the lack of evident structural or biochemical changes in the alimentary canal," he explains. "My strategy was to learn more about what is behind these conditions, particularly starting from the very basics, and focussing my attention on the innervation of the GI tract, one of the major control systems which can be altered in most of these functional bowel disorders." He goes on to summarise: "There are a number of mechanisms that should be investigated for a better understanding of pathophysiology and pharmacological treatment."

Prof De Giorgio would particularly like to see a far greater emphasis on one of the areas of interest that he currently sees as under-supported. This is the aforementioned topic of functional bowel disorders, and Prof De Giorgio expresses his view as to why there is a lack of research in this area. "One reason may be that functional bowel disorders are still poorly defined in terms of pathophysiology, and research should be devoted to decipher the complexity of the mechanisms that are underlying such conditions," he argues. An increase in research into functional bowel disorders is something that

Prof De Giorgio believes to be very important in order to gain an increased knowledge of such conditions to improve treatment options in the future: "I think this is very important because we need to have a better understanding of the mechanism including the visceral innervation in general."

Much of the research that is undertaken by the renowned gastroenterologist involves collaboration with medical professionals from other specialties, and this aspect of his work also formed part of our discussion. A prime example of this type of integration is observed with Prof De Giorgio's published research on the enteric nervous system: "I think that the research on the enteric system represents one of the classic examples of integration among scientists. Just to give you an idea, this neural system can be targeted by neurodegenerative disorders of the central nervous system. So this should prompt neurologists and gastroenterologists to work together in order to develop collaborative diagnostic and therapeutic programmes."

This theme of cooperation between members of the medical community is also seen in Prof De Giorgio's membership of several prominent gastroenterological societies, most notably the European Society of Neurogastroenterology and Motility and United European Gastroenterology (UEG). Of the latter, Prof De Giorgio speaks glowingly about the society's annual congress and its importance for those who work within the field throughout the world: "The aims of the society are to develop GI knowledge throughout the world, not only Europe of course. As a matter of fact I think we have the proof given by the something like 15,000 people attending the meeting pretty much every year. So these are really important numbers telling us how much the society is working well and the aims – educational, clinical, and scientific – are very well received throughout the world."

It is likely that collaboration across disciplines and major gastroenterological congresses like UEG Week will need to play a big role in the numerous challenges that gastroenterologists currently face. "I think that there are many areas that are growing with a very fast velocity," he answers when asked about what he believes to be the biggest issues in the field today. "One such field is GI oncology and diagnostic techniques, and of course treatments. So this is very important for the screening of colorectal cancer, and the diagnosis and treatment of colorectal cancer and a better understanding of many other forms of tumours. Neuroendocrine tumours represent one of the examples at the forefront of oncological research and clinical practice," states Prof De Giorgio.

It is clear that the causes of gastroenterological diseases are varied and complex, making treatments and prevention all the more difficult: "As a person who has been involved for many years in the field of GI, I think that rather than a single factor, I would suggest that a complex interplay exists between several mechanisms or factors, such as infections, genetics, other environmental factors, dietary factors, as well as other toxic agents," he says.

One way in which the general public can make a difference and better protect themselves against the onset of such conditions comes in the form of dietary factors. As can be understood from listening to Prof De Giorgio, however, there is no simple solution to improving the diet of the entire population. "We live in Italy, we have the Mediterranean diet. We all know that the Mediterranean diet is very important but nonetheless, as you may know, in Southern Italy we have huge problems of paediatric obesity, and this is again a very important cultural aspect which should be supported by public education," he explains.

Finally, we ask Prof De Giorgio what advice he has for medical students seeking to follow a career in gastroenterology. "This is a very nice question," he answers with a chuckle. "I would say to follow the inspiration that you have. Follow the enthusiasm that you have inside, the attraction that GI inspires in you, and of course, last but not least, to have a good mentor who emphasises and will increase these aspects that are inside you. So basically it is a delicate balance between what you have inside and what somebody else is able to pull out from you."

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ACHIEVING TREATMENT GOALS IN INFLAMMATORY BOWEL DISEASE: THE ROLE OF GUT-SELECTIVE THERAPY

Summary of presentations from the Takeda-sponsored symposia held at the 23rd United European Gastroenterology Week in Barcelona, Spain, on 26th and 28th October 2015

GUT-SELECTIVE BIOLOGIC THERAPY FOR ULCERATIVE COLITIS: LESSONS FROM SCIENCE AND PRACTICE

Chairperson

Gert Van Assche[1]

Speakers

Axel U. Dignass,[2] Britta Siegmund,[3] William J. Sandborn[4]

MANAGEMENT OF CROHN'S DISEASE: CURRENT CONCEPTS, FUTURE DIRECTIONS

Chairperson

Laurent Peyrin-Biroulet[5]

Speakers

James O. Lindsay,[6] Iris Dotan[7]

1. University of Leuven, Leuven, Belgium

2. Agaplesion Markus Hospital, Goethe University, Frankfurt, Germany

3. Charité-Universitätsmedizin Berlin, Berlin, Germany

4. Inflammatory Bowel Disease Center, UC San Diego Health System, La Jolla, California, USA

5. Nancy University Hospital, Vandœuvre-lès-Nancy, France

6. Barts Health NHS Trust and Queen Mary University of London, London, UK

7. Tel Aviv Sourasky Medical Center, The Sackler School of Medicine, Tel Aviv, Israel

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MEETING SUMMARY

Despite major advances in the inflammatory bowel disease (IBD) treatment landscape, the management of ulcerative colitis (UC) and Crohn's disease (CD) continues to pose challenges. There is significant scope to optimise treatment of IBD, and conventional therapies may fail to meet evolving treatment goals. Induction of remission with clinical control of symptoms and maintenance of remission with long-term prevention of disease progression are important considerations for healthcare professionals. The concept of complete remission integrates clinical remission, patient-reported outcomes, and mucosal healing, a key therapeutic goal for disease modification. The anti-integrin vedolizumab has been proven to be effective in inducing and maintaining clinical remission in IBD, both first-line and in tumour necrosis factor α (TNFα)-experienced patients, and has demonstrated mucosal healing benefits in UC patients. Safety remains critical for all therapies and vedolizumab is generally well-tolerated across all age groups, including the elderly. Real-world experience with vedolizumab has shown broadly comparable outcomes to the pivotal clinical trials.

GUT-SELECTIVE BIOLOGIC THERAPY FOR ULCERATIVE COLITIS: LESSONS FROM SCIENCE AND PRACTICE

Treatment Goals in Ulcerative Colitis: Clinical Remission and Beyond

Professor Axel U. Dignass

For the past 50 years, symptom control has been the predominant treatment goal in UC. However, as the range of available therapy options for UC has expanded, disease modification has emerged as a fundamental therapeutic aim in order to prevent complications and improve patients' quality of life (QoL). Optimising care has become increasingly complex within this evolving paradigm, creating a need for validated therapeutic targets to guide healthcare professionals making treatment decisions.

The clinical course of UC can vary greatly between different patients in terms of relapse patterns and severity.[1] Although no molecular or genetic biomarkers have been demonstrated to predict the disease course, a range of clinical characteristics have been correlated with long-term disease severity and outcomes. For instance, younger age at diagnosis, the presence of extensive disease, elevated inflammatory markers, requirement for systemic corticosteroids, treatment at initial diagnosis, and persistence of rectal bleeding have been identified as predictors of complicated disease.[2-4] These clinical markers can help to guide early therapy selection in patients with UC.

Response to therapy is another key clinical indicator, and endoscopically assessed mucosal healing may be particularly important in this context. The presence of mucosal healing following 1 year of treatment has been associated with reduced colectomy risk in patients with UC.[5] In contrast, a lack of mucosal healing following initial corticosteroid therapy in patients newly diagnosed with UC appears to predict a more aggressive disease course over the next 5 years, including elevated risks for colectomy, hospitalisation, and requirement for immunosuppressant therapy.[6] The definition of remission in UC has expanded to incorporate endoscopic control, with mucosal healing as a key therapeutic goal alongside control of clinical symptoms.

Despite these developments, there is significant scope to optimise treatment. Patients with UC often do not receive ideal medical therapy – for instance, experience from a US tertiary centre suggests that inadequate prescription or dosing of immunosuppressive therapy may commonly occur in clinical practice.[7] The clinical consequences of suboptimal treatment include disabling disease relapses, the development of complications that may require surgical intervention, and increased risk of colorectal cancer. It is essential to consider the potential impact of these events on a patient's day-to-day wellbeing, as well as their ability to continue working and socialising normally and any potential fertility issues.

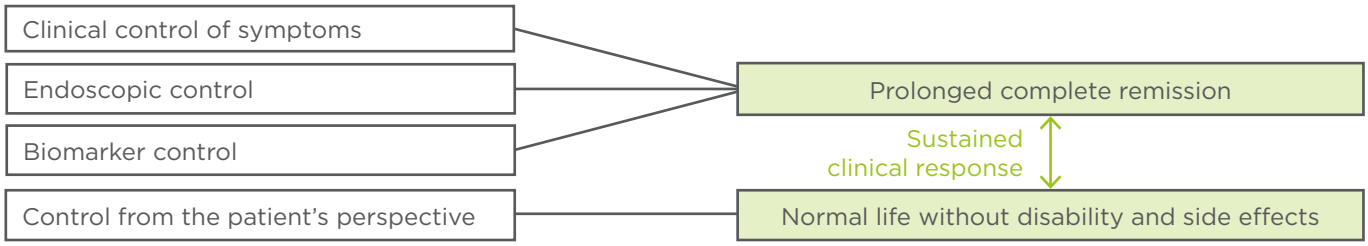

Figure 1: The evolution of treatment goals in ulcerative colitis.

Clinical practice guidelines play an important role in addressing suboptimal care, but may rapidly become outdated – for instance, the European Crohn's and Colitis Organisation (ECCO) 2012 guidelines for UC do not include newer agents such as vedolizumab,[8] as these guidelines are only updated every 4–5 years and include only evidence that has been published and thus peer-reviewed.

Enhancing patients' knowledge and engagement with therapy, for instance through shared decision-making, is increasingly recognised as a crucial way to improve outcomes, and is welcomed by patients. In a questionnaire-based study involving over 1,000 patients with IBD, 81% wanted to be actively involved in treatment decisions, and 50% expressed a need for close, equitable collaboration with their treating physician.[9] Incorporating patient-reported outcomes into therapeutic goals (Figure 1) helps to keep the patient at the centre of treatment, and may improve disease control and facilitate early detection of treatment failure.

In conclusion, the focus of treatment goals in UC now comprises long-term disease modification alongside clinical control of symptoms. The concept of complete remission, which incorporates endoscopic indicators such as mucosal healing with clinical remission (Figure 1), is central to this. Integrating patient-centred factors into treatment goals enables patients to be actively involved in their own care, and supports clinicians to understand what disease control means from each individual patient's perspective.

First-line Biologic Options for the Treatment of Ulcerative Colitis

Professor Britta Siegmund

Anti-TNFα agents, such as infliximab, adalimumab, and golimumab, and a humanised monoclonal antibody against the α4β7 integrin, vedolizumab, constitute the treatment options available for patients with UC stepping-up to biologic therapy. Efficacy, safety, and patient-related factors, such as clinical status and preference, are key considerations for clinicians selecting a first-line therapeutic strategy.

The efficacy profile of infliximab has been evaluated in two randomised, placebo-controlled studies, the Active Ulcerative Colitis Trials (ACT 1 and 2), which followed patients for up to 54 weeks (ACT 1) or 30 weeks (ACT 2).[10] Results at Week 8 demonstrated clinical remission rates of up to 40% and mucosal healing rates of approximately 60% following infliximab infusions (5 mg/kg) at Weeks 0, 2, and 6.[10] Significant improvements in patient QoL, expressed as the Inflammatory Bowel Disease Questionnaire (IBDQ) score, were also seen with infliximab compared with placebo, and were sustained up to Week 54 ($p<0.05$ for all comparisons).[11] The ACT 1 and 2 extension studies, which monitored long-term outcomes in patients continuing infliximab, showed that clinical remission was maintained in approximately 55% of patients after 3 years of infliximab treatment.[12]

Vedolizumab has also been shown to induce durable disease control. The GEMINI I study compared vedolizumab and placebo in two integrated, randomised, placebo-controlled studies that covered induction therapy up to Week 6 and maintenance therapy up to Week 52, respectively. Significantly higher rates of clinical response (47.1% versus 25.5%), clinical remission (16.9% versus 5.4%), and mucosal healing (40.9% versus 24.8%) were seen with vedolizumab compared with placebo at Week 6 ($p\leq0.001$ for all comparisons).[13] Further increases in clinical remission and mucosal healing rates were observed at Week 52 (Figure 2), and around 73% of patients completing the GEMINI I study demonstrated sustained clinical remission at 104 weeks.[14]

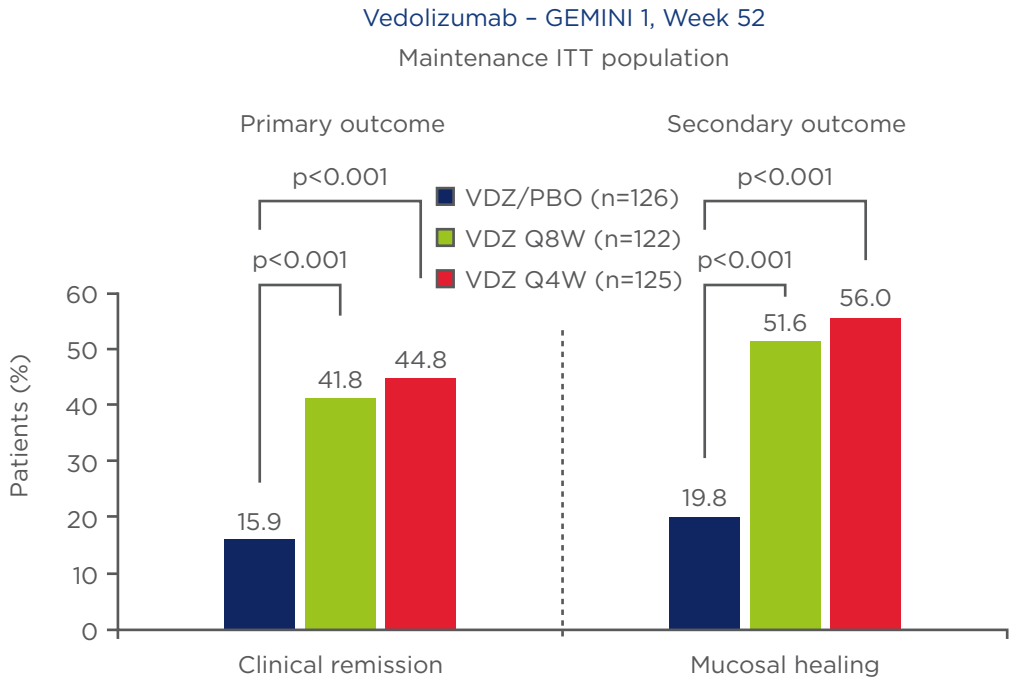

Figure 2: Clinical remission and mucosal healing rates at Week 52 with vedolizumab versus placebo.[13]
VDZ: vedolizumab; PBO: placebo; ITT: intention to treat; Q4W: every 4 weeks; Q8W: every 8 weeks.

Differentiating between infliximab and vedolizumab on the basis of their efficacy profiles is challenging, and other factors guide treatment selection in clinical practice, such as the speed of clinical response required. Infliximab demonstrates equivalent efficacy to ciclosporin over the first 7 days of treatment in patients with acute severe colitis,[15] whilst vedolizumab reduces intestinal inflammation more gradually and should not be viewed as a rescue therapy.

Safety is an essential consideration for all therapies, and a patient's specific comorbidities and their impact on the risk–benefit ratio of treatment are key factors. For instance, the risk of serious infections, such as reactivation of latent tuberculosis (TB) has been shown to increase with infliximab therapy.[16] Infections were rarely seen in the GEMINI I study,[13] and vedolizumab may be a suitable first-line option for patients at high risk of infection. All patients should be closely monitored for infection during treatment and prophylactic anti-TB therapy is indicated for patients diagnosed with latent TB during pre-treatment screening.

In addition, the relative risks and benefits of treatment should be viewed from the patient's perspective. The majority of patients want to be involved in treatment decisions,[9] and some patients, particularly those with severe disease, may be prepared to accept greater treatment-associated risks than others.[17] A process of shared decision-making, involving patients at every step of the process, is an essential element of treatment selection for clinicians prescribing first-line biologic therapy.

Real-World Experience with Gut-Selective Therapy in Ulcerative Colitis

Doctor William J. Sandborn

Post-regulatory studies performed following the approval of vedolizumab in 2014 have demonstrated broadly comparable outcomes between the pivotal trial and clinical practice settings. In addition, real-world experience with vedolizumab has generated valuable practical insights around its clinical use, and highlighted key areas for future investigation.

Preliminary data from an analysis of patients with active moderate-to-severe UC treated in a large, multicentre, US consortium (n=59) has captured some aspects of real-world experience with vedolizumab. Progressive improvements in clinical response, clinical remission, and mucosal healing rates (Figure 3) were observed up to 30 weeks,[18] and appear to be at least equivalent to the outcomes seen in the GEMINI I study. These results are

consistent with data from a variety of other studies across the US and EU, which have demonstrated Week 14 clinical response rates of around 40–60%, and clinical remission rates of approximately 20–40%.[19-23]

A range of benefits beyond overall clinical response have been delineated by the GEMINI I study, and are supported by real-world clinical experience. For instance, as well as showing efficacy as a first-line biologic, vedolizumab has shown a consistent signal of clinical response across subgroups of patients who have received different prior therapies, including corticosteroids, immunomodulators, and anti-TNFα agents.[24] Patients in the multicentre US consortium study were frequently pretreated; the majority had received at least one prior anti-TNFα therapy (75%),[18] suggesting that vedolizumab may be effective across these groups. Vedolizumab also demonstrates efficacy across different patient age groups, including elderly individuals, in both GEMINI I and post-regulatory studies.[18,25,26]

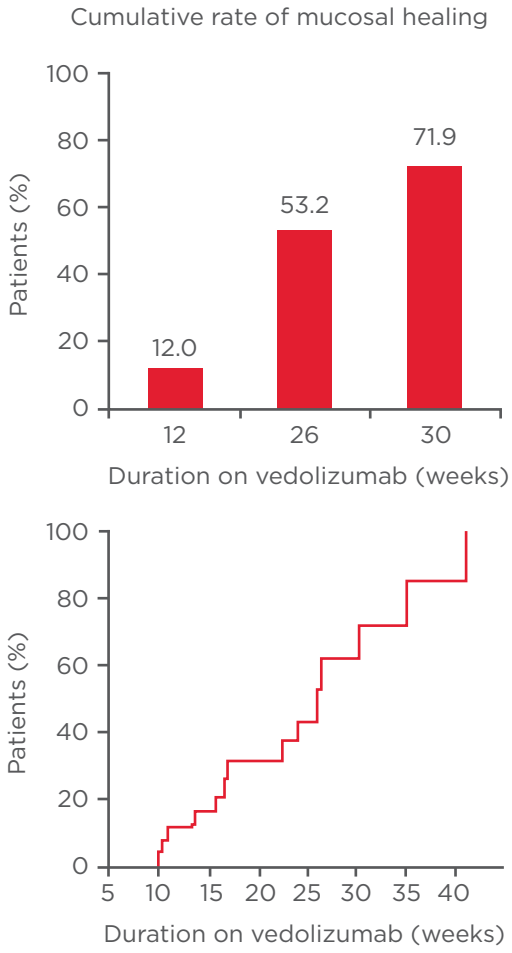

Figure 3: Mucosal healing rates in ulcerative colitis patients treated with vedolizumab in a multicentre US consortium study.[18]

GEMINI I also demonstrated a corticosteroid-sparing effect for patients receiving vedolizumab, with 74% of patients experiencing corticosteroid dose reductions and 39% being corticosteroid-free by Week 52 of therapy, compared with 57% and 19% of the patients receiving placebo, respectively.[27] In a French observational study, 45% of patients achieving a clinical response were corticosteroid-free following 14 weeks of vedolizumab therapy.[23]

Real-world experience of vedolizumab's safety profile has been consistent with results from the clinical trials, including common adverse events involving the joints and an acneiform rash, which appeared to be self-limiting.[28] Although infectious events occurred in around 7–11% of UC patients,[18,23] no clear signal for serious or opportunistic infections or cases of progressive multifocal leukoencephalopathy (PML) have been seen. Taken together, no new safety signals have been identified by post-regulatory studies,[18] with the limitation that there are currently no data available on the safety of vedolizumab in pregnancy.

Further investigation is also needed around vedolizumab's immunogenic potential. Antibodies to vedolizumab were detected in 3–4% of patients receiving induction and maintenance therapy in the GEMINI I study,[29] but the clinical impact of these antibodies and the role of concurrent immunosuppressive therapy to prevent their formation remain incompletely understood. Other key areas requiring further study include the development of drug monitoring techniques, and combination use of vedolizumab with other medical therapies in UC. Real-world experience with vedolizumab is currently in its early stages, and continued development of this body of evidence will provide further insights around its optimal use in clinical practice.

MANAGEMENT OF CROHN'S DISEASE: CURRENT CONCEPTS, FUTURE DIRECTIONS

Treatment Goals in Crohn's Disease

Doctor James O. Lindsay

As the treatment landscape in CD has transformed to include biologic therapies alongside steroids and immunomodulatory agents, treatment goals have evolved to incorporate long-term disease modification with the more traditional aim of clinical remission. Most recently, the emergence of

mechanistically novel agents such as vedolizumab and development of more affordable anti-TNFα biosimilars have expanded the range of biologic agents available for CD. However, questions remain about how clinicians can optimise their use of biologics at every stage of CD management and support patients to achieve their therapeutic aims. Selecting the right drug for the right patient is essential, and both safety and patient preference are key considerations alongside efficacy.

Although good symptomatic control is critical, clinicians should prioritise disease modification and prevention of complications in their long-term management of patients with CD. The transmural nature of intestinal inflammation in CD can lead to progressive formation of strictures and penetrating lesions necessitating surgical resection, and the possibility of stoma formation. In addition, progressive disease negatively impacts patients' overall wellbeing. In a questionnaire-based study of over 500 patients with IBD, individuals with CD reported lower health-related QoL than either patients with UC or the general population.[30]

Traditionally, clinical remission has been used to define treatment response, but clinical symptoms may not accurately reflect ongoing inflammation. For instance, the randomised SONIC trial, which compared infliximab and azathioprine combination therapy with each agent alone in biologic and immunosuppressant-naïve patients with CD, showed that around 43% of patients in clinical remission still had evidence of active mucosal disease.[31] In this context, mucosal healing has become a key therapeutic aim orientated towards disease modification. Clinical trial endpoints for IBD therapies have also evolved to reflect this shift in treatment goals, with mucosal healing and patient-focussed measures of disability becoming increasingly important considerations.

Clinicians should tailor their approach to individual patients using a range of different treatment strategies.[32] For some patients, conventional step-up care is appropriate; other patients may require a more aggressive approach, using immunomodulatory agents at diagnosis and stepping-up to a biologic if these fail. Initiating biologics at diagnosis as part of a top-down treatment strategy may be suitable for patients with severe disease. Currently, no predictive biomarkers exist to guide treatment selection in CD, although a range of clinical features have been associated with disease progression. These include the presence of extensive small bowel disease, severe upper gastrointestinal or rectal disease, complex perianal disease, deep colonic ulcers, and early development of strictures.[33-36]

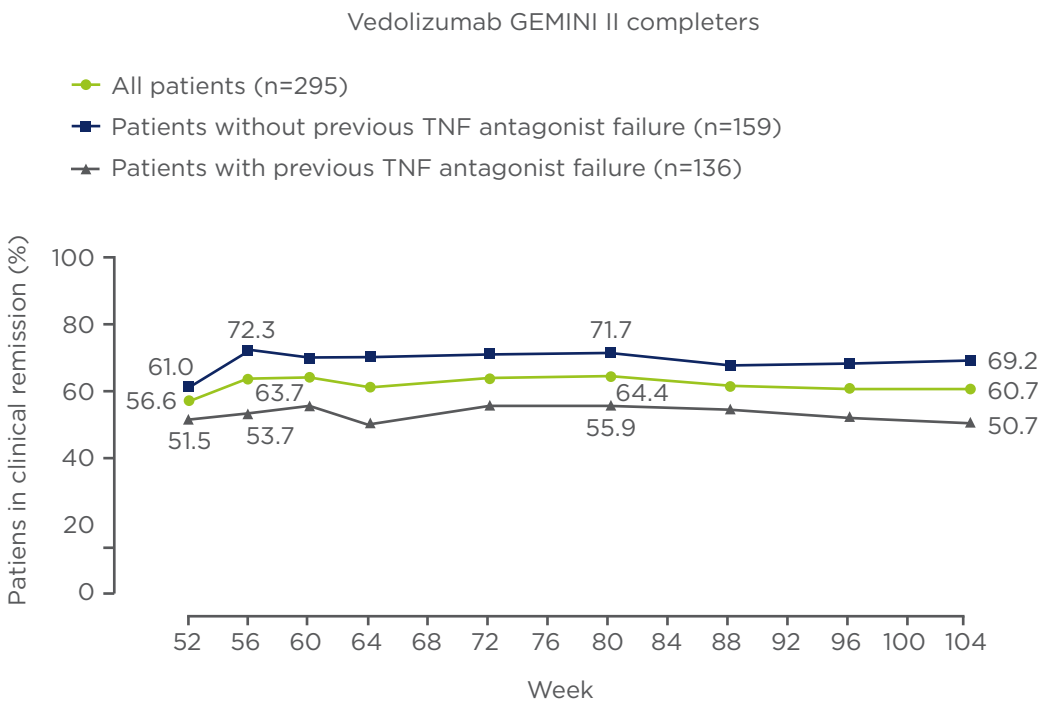

Figure 4: Clinical remission rates in the GEMINI II extension study.[39]
TNF: tumour necrosis factor.

Regardless of whether an anti-TNFα or an anti-integrin agent is selected, early treatment initiation plays a key role. For instance, 57% of patients in the SONIC trial achieved steroid-free remission at Week 26 of infliximab and azathioprine combination therapy;[37] early biologic therapy may have contributed to this high treatment response rate, as the median disease duration at trial entry was around 2 years. Durable treatment responses have also been observed with the anti-integrin agent vedolizumab, although these may develop more gradually than with anti-TNFα agents. A *post hoc* analysis of the GEMINI II study, which compared vedolizumab with placebo in patients with active moderate-to-severe CD, demonstrated that around 22% of patients who were classified as non-responders at Week 6 of the study subsequently developed a treatment response, which was maintained at 1 year.[38] The GEMINI II extension study showed that patients receiving vedolizumab remained well over the course of the subsequent 2 years, whether or not they had previously failed an anti-TNFα agent (Figure 4).[39]

The role of combination therapy at treatment initiation with vedolizumab remains to be defined. However, co-administering steroids may help to bridge the induction period. In the GEMINI II study, a higher proportion of patients treated with vedolizumab and corticosteroids achieved clinical remission at Week 6 compared with placebo or with patients treated with vedolizumab and an immunomodulator.[40] In addition to focussing on efficacy, safety is a key consideration at every stage of a patient's treatment pathway. Infection-related complications are a particular concern with biologic therapies in CD. A recent meta-analysis indicated that the risk of developing an opportunistic infection is not increased with anti-integrin use.[41] In contrast, anti-TNFα therapy carries an approximately 2-fold increased risk of opportunistic infections.[42]

To optimise care in the long term, clinicians should objectively monitor the effects of treatment in both symptomatic and asymptomatic patients. Timeframes for treatment response are drug-specific, and can take up to 12 weeks to manifest in patients receiving vedolizumab. Before switching to a different agent, efforts should be made to exclude the emergence of new complications and to optimise existing therapy, for instance through checking patient adherence to treatment and dose modification guided by therapeutic drug monitoring. A multidisciplinary 'virtual clinical' approach, where key blood results and drug doses are regularly reviewed, can help to streamline patient monitoring and facilitate optimisation of therapy.

Overcoming Treatment Challenges in Crohn's Disease

Doctor Iris Dotan

Healthcare professionals caring for patients with CD face a complex range of challenges in improving their long-term outcomes. Around 50% of these patients are candidates for biologic therapy, and selecting between different agents for first-line therapy, managing intolerance or safety issues, and switching agents in patients who do not respond or lose their initial response to therapy (defined as primary and secondary non-responders, respectively) pose key concerns.

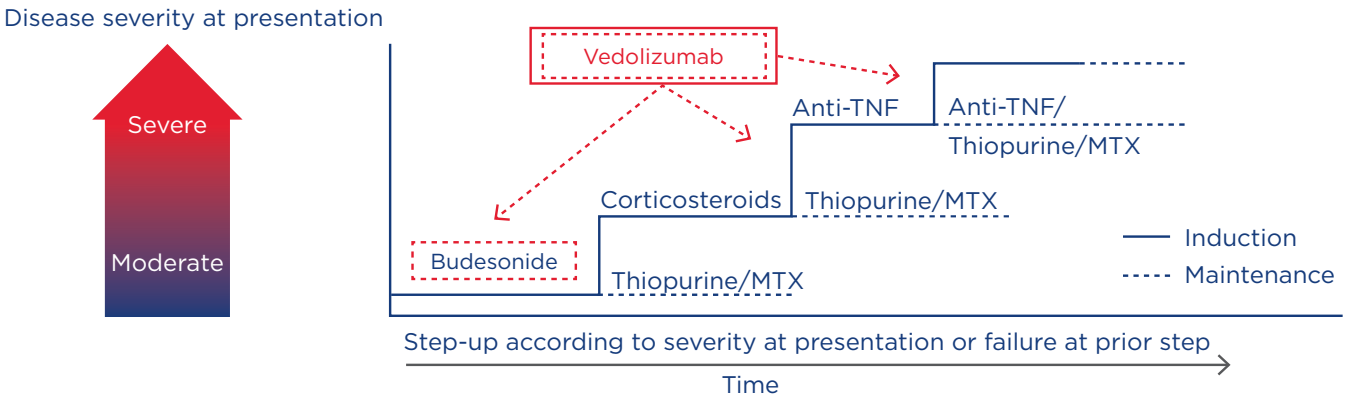

Figure 5: Potential positioning of vedolizumab in Crohn's disease.
TNF: tumour necrosis factor; MTX: methotrexate.

Real-world practical guidance can support clinicians to address these challenges in the context of their patients' long-term treatment goals.

When initiating biologic therapy, careful selection of a first-line agent is critical since treatment efficacy may decrease with subsequent lines of therapy. The GEMINI II study demonstrated higher clinical remission rates with vedolizumab in the maintenance phase of therapy in patients who had previously failed an anti-TNFα agent compared with anti-TNFα-naïve patients.[43] These findings are reflected by both a recent meta-analysis and real-world experience with vedolizumab from a US tertiary referral centre.[21,44] In a further post-regulatory study published as an abstract, clinical markers of disease activity were observed to improve as early as 2 weeks after starting vedolizumab in patients who had previously received anti-TNFα therapy.[45]

As well as being a potential option in anti-TNFα-experienced patients, re-treatment with vedolizumab appears to be safe and effective, as indicated by data from the GEMINI II extension study in patients who continued or re-started therapy following the trial's conclusion.[46] Vedolizumab also demonstrates a positive treatment effect in more aggressive phenotypes, such as fistulising disease. In patients with draining fistulae at entry to the GEMINI II study, the majority of whom had perianal disease, fistula closure rates at Week 14 were 28% in patients receiving vedolizumab induction and maintenance therapy compared with 11% in patients receiving vedolizumab induction therapy and placebo during the maintenance period.[47]

Patients who do not respond adequately to anti-TNFα therapy can be a particularly challenging group to treat. In both primary and secondary non-responders, changing to an agent in a different class may be more beneficial than an in-class switch. For instance, in a retrospective study from a European tertiary referral centre of IBD patients with primary non-response to anti-TNFα therapy (75 with CD), clinical remission without the need for drug discontinuation was seen in 31% of patients switching to another anti-TNFα and 40% of patients switching to vedolizumab. However, the need for IBD-related surgery was 63% for in-class switch and 43% for out-of-class switch.[48] In patients with secondary non-response to anti-TNFα agents, in-class switching can result in some restoration of clinical response,[49,50] although a retrospective analysis of patients treated with a third anti-TNFα agent showed that only 33% of patients remained on treatment at 1 year.[50] This may indicate that in-class switching may not address patients' requirements for long-term therapy.

In the context of anti-TNFα non-response, an out-of-class switch to vedolizumab may be an appropriate option. Data from the randomised GEMINI III study, which evaluated vedolizumab induction therapy in patients with active moderate-to-severe CD, showed enhanced clinical response (CDAI-100) rates of 47% at Week 10 in patients who had previously failed anti-TNFα treatment.[51] Post-regulatory experience with vedolizumab further supports this concept. In a prospective, European, tertiary referral centre study in a small group of patients with treatment-refractory CD, half of whom had failed at least three previous anti-TNFα agents, clinical remission rates of 54% were observed 6 weeks after switching to vedolizumab.[19]

In addition to efficacy, monitoring and management of safety issues are of paramount importance in all patients receiving biologic therapy. Elderly patients may be at greater risk of adverse events associated with anti-TNFα therapy, primarily infectious complications.[52-54] Vedolizumab may be a relevant choice for these patients; a *post hoc* analysis of the GEMINI II study demonstrated similar Week 52 clinical remission rates and adverse event rates between patients older than 55 years and younger patients.[55] In addition, no specific safety signals for serious infections such as PML have been observed with vedolizumab, which may reflect this agent's gut-selective inhibition of leukocyte trafficking.[56]

Although the need for predictive biomarkers to guide selection of biologic therapies remains, both clinical trial data and real-world experience with these agents can guide clinicians to choose the right treatment for each patient and address specific treatment challenges. Vedolizumab is a key addition to the biologic armamentarium, and is a relevant therapeutic option across a wide spectrum of clinical presentations (Figure 5) and patient subgroups in CD.

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BIOLOGIC THERAPIES: FROM COMPLEXITY TO CLINICAL PRACTICE IN A CHANGING ENVIRONMENT

This symposium took place on 27th October 2015 as part of the United European Gastroenterology (UEG) Week 2015 in Barcelona, Spain

Chairperson

Remo Panaccione[1]

Speakers

Remo Panaccione,[1] Geert D'Haens,[2] Brian Feagan[3]

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MEETING SUMMARY

This symposium provided an opportunity for global experts to discuss the challenges posed by the introduction of biosimilars. The impact of the manufacturing process on clinical outcomes, maintaining

treatment responses over the long term, and issues surrounding patient management in a changing environment were addressed.

The symposium was opened by Prof Panaccione describing the evolution of inflammatory bowel disease (IBD) treatment in the last 20 years and how biologics have improved outcomes. Prof D'Haens provided an explanation of the complexity surrounding biologic drug development and the hurdles facing drug manufacturers when ensuring high quality and consistently performing products over time. Prof Panaccione discussed the clinical challenges in balancing the transition from induction to maintenance therapy in order to provide a clinically relevant and sustained response to therapy. He also discussed the evidence for long-term outcomes with adalimumab for IBD. Prof Feagan highlighted the issues faced by clinicians treating patients with biologics, including the ability to switch between biologics without loss of efficacy or impact on safety, and the need to consider interchangeability between biologic therapies and the potential risk and impact of immunogenicity.

Evolution of Therapeutic Progress in Inflammatory Bowel Disease

Professor Remo Panaccione

Biologics have had a significant impact on the treatment of many serious inflammatory diseases, including Crohn's disease (CD) and ulcerative colitis (UC). Their use has resulted in significant improvements in outcomes, including patient quality of life (QoL), and has enabled self-care and the ability to return to work for many patients.

CD and UC significantly affect patient health and QoL. Before the advent of anti-tumour necrosis factor treatments (anti-TNFs), patients were typically chronically hospitalised with a stoma and required total parenteral nutrition. Patients themselves often expressed that they felt ashamed, afraid, and had a lack of control of their disease, and some became very desperate and without hope.

Treatment goals have been redefined with the advent of biologic therapies such as recombinant receptor–Fc fusion proteins, e.g. abatacept and etanercept; monoclonal anti-TNFs, including chimeric, humanised, and human forms; and the pegylated Fab fragment, e.g. certolizumab pegol.[1] These drugs are clinically effective and have a rapid onset of action, and lead to improvements in QoL.[2-8] In patients with IBD, new treatment targets now include mucosal healing: the ability to induce and maintain clinical remission and improvements in serum or faecal biomarkers, such as C-reactive protein and faecal calprotectin.[9]

The therapeutic pipeline includes several biologic therapies outside the anti-TNF class, including interleukin inhibitors, cell adhesion molecule inhibitors, JAK3 inhibitors, chemokine receptors, immunomodulators, and stem cell therapies.[10] In the next 3–5 years, at least two or three new classes of biologics are expected to become available, as well as biosimilars of current reference products. These new drugs bring their own challenges in terms of their ability not only to demonstrate efficacy, safety, and tolerability, but also to address the complex and robust manufacturing and production processes required for biologics.

Biologic Therapy Complexity and Insights Into Manufacturing

Professor Geert D'Haens

When developing a biosimilar, comparable quality, safety, and efficacy to the reference product needs to be demonstrated. The European Medicines Agency (EMA) has stated that a biosimilar sponsor *"is to generate evidence substantiating the similar nature, in terms of quality, safety, and efficacy, of the new similar biological medicinal product and the chosen reference medicinal product authorised in the community."*[11] Equally, the US Food and Drug Administration (FDA) stated that a *"biologic product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components"* and *"No clinically meaningful differences exist between the biologic product and the reference product in terms of the safety, purity, and potency."*[12]

It is important to recognise that biosimilars are similar to the reference product, but are not necessarily the same. The challenge is to establish if minor differences between biosimilars and reference products could lead to changes in clinical or pharmacological effects. Regulators very closely monitor the manufacturing processes of all biologics, which is a very delicate and complex

procedure and is affected by many factors, including the duration of cell culture, pH, temperature, and culture media, as well as how much oxygen and how many nutrients are added to the culture.[13,14] Other factors that influence the properties of the product include how much host-cell DNA is removed in the process and immunogenic influences. This complexity means that drugs are produced in batches, with the goal of ensuring homogeneity within a batch and consistency between batches.

Not surprisingly, the biologics that have been on the market the longest have had the greatest number of changes over time. Remicade® (infliximab) has had more than 35 manufacturing changes in its lifetime, including new purification methods and setting up of a new manufacturing site, which can affect the manufacturing technique, cell culture medium, and where cells are grown.[15,16] Enbrel® (etanercept; not licensed for IBD) has also undergone changes in its manufacturing procedures over time, with a resulting modification in the number of basic versus acidic variants, which can impact efficacy and antigenicity.[15]

To determine whether changes incurred in the manufacturing process affect the efficacy of a biologic, it is important to understand how the drug acts. This can be challenging because the mechanism of action of anti-TNFs is not fully understood. Within the structure of a therapeutic antibody, the Fab fragment is the most active component. It is known to bind soluble TNF that is freely circulating in the body and mucosae, but there can be differences between anti-TNFs with regard to the avidity and affinity of binding.[16] Anti-TNFs also bind to cells on which TNF is exposed on the cell membrane, and this binding induces cell apoptosis.[17-19] Antibodies also have an Fc 'tail', which may have biologic effects and can have a significant impact on the elimination and half-life of the molecule. The Fc tail is typically where sugars adhere to, but it may also bind to other cells. Experimentally, adalimumab and infliximab, which have an Fc tail, stimulate the conversion of monocytes into macrophages, which themselves decrease lymphocyte proliferation (Figure 1).[20]

This does not occur with certolizumab, which does not have an Fc tail and lacks this activity. However, when a version of certolizumab with an Fc tail was tested, it had a similar effect on lymphocyte proliferation to that seen for adalimumab and infliximab.[20] Post-translational modifications, e.g. glycosylation resulting in folding of the molecule, can also occur.[20] These modifications can lead to changes in the sugars and lysine groups, which in turn can alter the efficacy and safety of the biologic. Adalimumab is a recombinant IgG1 glycoprotein containing 1,330 amino acids, and which has high specificity for human TNFα.[21] Adalimumab has been manufactured since 1997 and the number of indications for which it is used has increased over time. The manufacturing process has also changed as the scale of production increased.[22] To counter this, the robustness of the manufacturing process has become more stringent to ensure no differences occur in the batches produced over time and also between different factories.[22] The cell line, cell culture media, and the steps taken to purify the molecule have remained the same.[22]

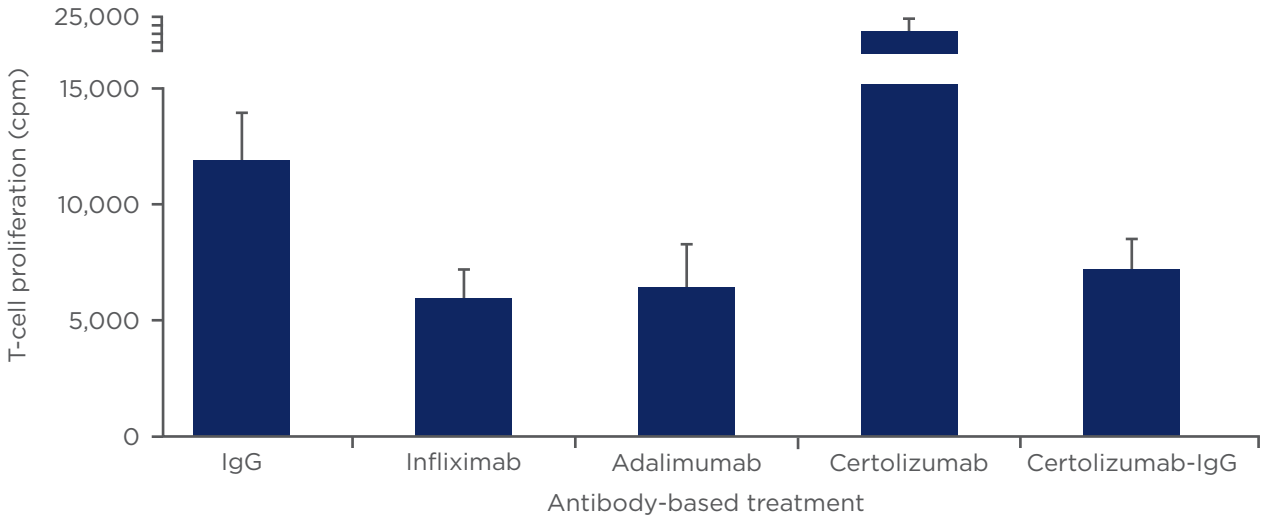

Figure 1: Effect of the Fc region on T lymphocyte cell proliferation.[20]

In summary, structure has an impact on function and is related to the post-translational modification of the protein. The production of biologics is complex: all biologics have inherent heterogeneity and can vary in terms of their immunogenic potential. In addition, some biologics may have significant batch variations. Any of these factors can impact on drug efficacy and safety if not carefully controlled.

Maintaining Sustained Inflammation Control in Inflammatory Bowel Disease

Professor Remo Panaccione

With the advent of anti-TNF therapies, treatment goals have evolved from simple response to remission, including clinical remission, mucosal healing and, possibly in UC, histological remission.[23] Regardless of the goals that are aspired to, what is truly needed is sustainability of treatment response. This is currently managed with induction therapy followed by a decrease in the dosage by either decreasing treatment intensity or increasing the interval between doses. One of the challenges is determining the length of the induction period, which is not necessarily addressed in clinical trials.

In the Phase III, randomised, double-blind, placebo-controlled CHARM (Crohn's trial of the fully Human antibody Adalimumab for Remission Maintenance) study, which investigated the efficacy of adalimumab maintenance therapy in patients with moderate-to-severe CD, patients received adalimumab induction therapy (80/40 mg) at Weeks 0 and 2 and were subsequently randomised to receive 40 mg every other week, 40 mg weekly, or placebo through Week 56.[24] The primary endpoint was the rate of randomised responders (defined as a CD activity index [CDAI] decrease ≥70 points at Week 4) who achieved clinical remission (CDAI <150 points) at Weeks 26 and 56. The percentage of randomised responders was 58% at Week 4, still leaving a substantial number of non-responders. However, if the induction period was increased to 12 weeks in the initial non-responders, 60% went on to achieve clinical remission,[25] which mimics what is seen in clinical practice. In terms of long-term maintenance of remission (4 years), this was achieved in 84% of observed patients, 80% using last observation carried forward (LOCF), and 54% using hybrid non-responder imputation analysis (Table 1).[26] Similar results were seen in a subset of patients who had fistulae at baseline.

Comparable results were reported in patients with active moderate-to-severe UC treated with adalimumab. In the ULTRA-3 open-label extension study, patients in remission at the end of the ULTRA-1 and ULTRA-2 studies were followed beyond Week 52.[27] In ULTRA-3, approximately 80% of patients continued to be in remission up to Week 156 and 82% maintained mucosal healing up to Week 144, according to LOCF analysis. In addition, approximately 60% of patients were steroid-free at Week 208, and hospitalisation and surgical rates decreased in Years 1, 2, and 3. These results demonstrated that remission and mucosal healing rates were maintained after 4 years of adalimumab therapy, and were associated with low colectomy and hospitalisation rates and improved QoL.

In terms of explaining the sustainability of the response to adalimumab therapy, pharmacokinetic studies have shown that the difference between peak and trough is extremely small and therefore the variability in the individual patient may be very low.[26] This contrasts with infliximab treatment every 8 weeks, which is associated with much more variability in the peak and trough levels;[28] the latter is thought to increase the risk of immunogenicity.

Table 1: Adalimumab long-term maintenance of remission in Crohn's disease.[26]

	Patients in remission, % (n)			
Weeks from baseline	**80**	**104**	**164**	**212**
hNRI analysis	77.2 (112/145)	77.2 (112/145)	64.8 (94/145)	53.8 (77/145)
LOCF analysis	82.1 (119/145)	86.2 (125/145)	82.8 (120/145)	80.0 (116/145)
As-observed analysis	83.0 (112/135)	86.8 (112/129)	84.7 (94/111)	83.8 (62/74)

hNRI: hybrid non-responder imputation; LOCF: last observation carried forward.

The ongoing MOSAIC study may provide more information regarding the relationship between the variability in peak and trough levels and possible subclinical inflammation in the near future.

As long-term use of anti-TNF therapies becomes accepted practice, risk assessment requires an understanding of their long-term safety. Analysis of long-term safety across a number of indications for adalimumab (almost 12 years of exposure) in over 23,000 patients demonstrated individual differences in rates according to disease populations.[29] However, no new safety signals were reported and the safety profile was consistent with what was already known regarding the anti-TNF class.

There have also been results from the ongoing, multi-centre, uncontrolled, 6-year, non-interventional Pyramid registry, which was designed to evaluate the long-term safety of adalimumab as it is used in routine clinical practice in patients with active moderate-to-severe CD.[30] The registry includes patients who participated in clinical trials, as well as patients prescribed adalimumab post-marketing. It includes 424 sites in 24 different countries and, as of December 2014, there were more than 5,000 registered patients, with a retention rate of approximately 60%. At the end of the study, 5–6 years of exposure data for more than 25,000 patients is expected. Thus far, only 14% of patients have withdrawn from the registry due to lack of efficacy and 7% have withdrawn due to adverse events. These results corroborate with observations in the pivotal studies.

In summary, adalimumab has been shown to have a sustained efficacy for up to 4 years in both CD and UC; it has been shown to be safe and well tolerated in both maintenance studies and safety registries. The small variability in peak and trough levels may be responsible for these results and are being explored further.

Patient Management: Strategies and Challenges in a Changing Environment

Professor Brian Feagan

Patient management faces the challenge of interchangeability, due to multiple non-medical switching by a pharmacist. The primary concerns for patients are efficacy and safety. This situation is a provocative manoeuvre for formation of anti-drug antibodies. Accordingly, a patient in stable remission is unlikely to want to switch to another product, no matter how similar it is, because of concerns over changes in efficacy and safety, and physicians share these concerns. The primary reason for switching to a biosimilar is cost savings to payers and society, which can create a tension between the individual's rights, expectations as a patient, and the broader societal need.

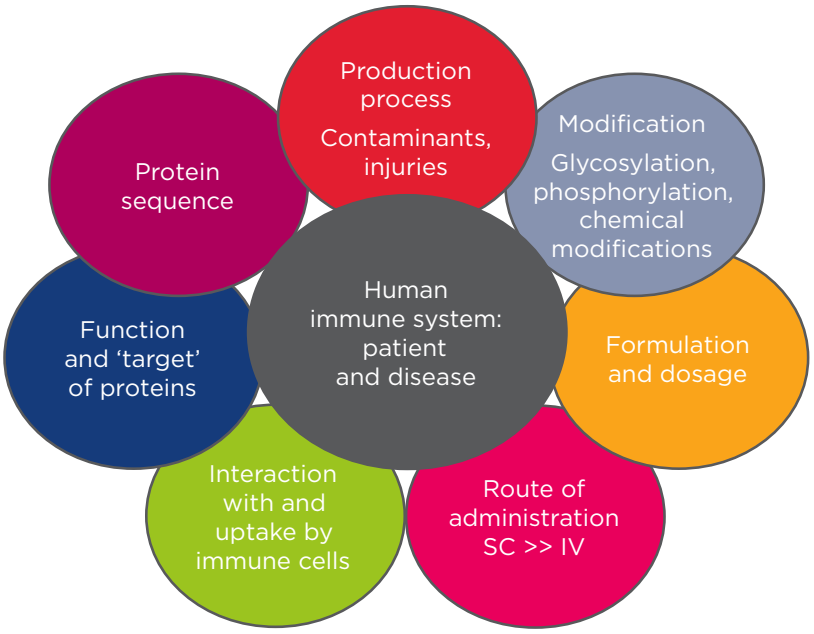

Figure 2: Product-related factors contribute to the immune response.[42,43]
IV: intravenous; SC: subcutaneous.

In terms of clinical evidence and durability of response, there is a wealth of data for reference drugs, which is reassuring for prescribers and physicians. This contrasts with biosimilars, which have little data on patient experience before they come to market.

There are two types of switching: (1) medically relevant switching due to lack of efficacy or because of adverse events. The challenge is establishing how to manage these patients; switching within a drug class or outside a drug class is often considered. Controlled data for current drugs is available to help decision-making,[31-34] but is often not available for biosimilars; (2) non-medical switching occurring because of preference issues for the patient, which have nothing to do with efficacy or safety, or because of the need for cost savings in the case of biosimilars. The lack of clinical data renders it difficult to assess the clinical and health economic consequences of this practice.[35]

In an assessment of 754 patients with CD, UC, ankylosing spondylitis, psoriasis, or psoriatic arthritis who underwent non-medical switching between different anti-TNFs, switchers were less well controlled than continuers (47% versus 88%).[36] Inpatient stays and emergency department visits were also greater in switchers versus continuers (5.0 versus 3.4 and 14.3 versus 4.2, respectively).[33]

In a different disease area, a systematic review of 58 clinical trials in which more than 12,000 patients were switched between classes of erythropoietin, growth hormone, or granulocyte-colony stimulating factor concluded that patients could be safely switched from one product to another.[37] However, most of the clinical trials were not designed to identify switch-related adverse events and some studies only followed up patients after they were switched in single-arm, open-label studies.

With regard to anti-TNF therapy and switching to biosimilars, the EMA, FDA, and Health Canada have all indicated that there is insufficient evidence to draw any conclusions regarding the safety of non-medical switching, but they also state that this issue is not within their jurisdiction. Ultimately, policy decisions will be made at a regional level, which is not ideal.

Immunogenicity is potentially the most serious consequence of multiple switching. All foreign proteins have the potential to be immunogenic.[38] The immune response is a complex, unpredictable process[39,40] that is governed by multiple factors (Figure 2).[41,42] Tertiary and quaternary protein structures govern whether T cells react, sensitise, or tolerise. This consideration has raised some concerns regarding the immunogenicity of biosimilars. At the last count there were nine biosimilar infliximab molecules under development. No high-quality clinical data are available to evaluate the consequences of interchangeability of these products.

The development of antibodies to a drug being administered is a concern because they can neutralise the biologic effect, impair drug pharmacokinetics, and cause hypersensitivity reactions. In patients who developed antibodies to infliximab, a shorter duration of therapeutic response was observed.[43] These patients were also more likely to develop hypersensitivity reactions and infusion reactions.[43] Sensitisation is also an issue for humanised anti-TNFs such as adalimumab, with approximately 20% of rheumatoid arthritis patients developing anti-drug antibodies.[44] In these patients, a high titre of antibodies was associated with low drug concentrations and reduced clinical efficacy.[45]

Changes in the manufacturing process can rarely result in autoimmunity. Cases of pure red-cell aplasia (PRCA) have been reported in patients treated with recombinant erythropoietin who developed anti-erythropoietin antibodies.[45] The cause was a change in the plasticiser present in syringe stoppers, which resulted in adjuvant activity and the formation of anti-erythropoietin antibodies.[46] More recently, multiple cases of PRCA have been reported in Thailand as a result of autoantibody development to biosimilar erythropoiesis-stimulating agents manufactured in India.[47]

The Phase IV NOR-SWITCH study, funded by the Norwegian government, has been designed to assess the efficacy and safety associated with non-medical switching between Remicade (infliximab) and the biosimilar Remsima™ (infliximab) in 18 hospitals.[48] The study has enrolled 500 patients with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, UC, CD, and chronic plaque psoriasis and will be completed in May 2016. Concerns regarding this study include the small patient numbers, which compromise the validity of the non-inferiority design, and the fact that the trial only assessed a simple substitution and not multiple switches between agents. In an ideal world, a study needs to address the impact of multiple switching to reflect what is likely to

happen in clinical practice when biosimilars become widely available.

In summary, the use of biosimilars is increasing but further data are needed to assess their efficacy and safety. The potential for immunogenicity should be considered when deciding upon the use of a biosimilar instead of its originator biologic or when switching between biosimilar products.

Q&A session

What kind of studies need to be done to address immunogenicity issues?

Prof Feagan stated that studies would need to include a sufficient numbers of switches (4 or 5) of sufficient duration (1–2 years) in the case of infliximab, where the half-life is 12–14 days, with switch intervals of around 4–6 months.

On what basis did Health Canada decide not to extrapolate into IBD for the infliximab biosimilar?

Prof Panaccione replied that the Health Canada position for not extrapolating into IBD was based on structure and function. There are data that suggest the Fc tail may be associated with antibody-dependent cytotoxicity which, in turn, may be associated with some therapeutic efficacy in CD and possibly in UC. They also cited a few safety concerns.

What kind of data, or how much data, would be required to recommend the use of a biosimilar in IBD?

Prof Feagan replied that he would accept index extrapolation in most situations. In order to extrapolate across indications, it is important to choose the indication that is most capable of differentiating between the biosimilar versus the reference product and to choose a sensitivity assay. In the case of the biosimilar infliximab, measurement of ACR20 scores in patients with rheumatoid arthritis was chosen, but Prof Feagan felt that this assay was not sensitive enough. Prof D'Haens added that there is currently only one biosimilar in Europe, Remsima (infliximab), and that the data, despite being limited, showed that it was equally as effective as Remicade (infliximab). In the future there could be ≥8 biosimilar infliximab molecules to choose from. If the choice is based only on cost, then every year a different company may win the tender and patients would have to be switched to a new infliximab without fully understanding the clinical and immunogenic consequences.

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THE FULL PICTURE OF ULCERATIVE COLITIS: THE BURDEN, THE PATIENT, THE TREATMENT

This symposium took place on 26th October 2015 as part of United European Gastroenterology (UEG) Week 2015 in Barcelona, Spain

Chairperson

Julián Panés[1,2]

Speakers

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MEETING SUMMARY

Ulcerative colitis (UC) carries a significant, progressive disease burden that is often underestimated or misinterpreted by healthcare providers. Adverse outcomes have a major impact on patient quality of life, with a significant burden of symptoms both during and between inflammation flares. Chronic, uncontrolled disease leads to epithelial fibrosis and 'lead pipe' colon, dysplasia, and potential colonic cancer. Healthcare providers and patients share similar treatment goals, even if these are not verbalised in the same way, and clinicians need to fully understand the issues most important to patients. Understanding and collaboration can improve identification of meaningful treatment goals and overall disease management. In real-world practice, patients should be categorised according to disease characteristics and prognosis, and managed with appropriate, optimised therapies. Early, top-down management should be implemented in high-risk patients and all patient-centric therapeutic decisions made within the context of a full benefit/risk assessment.

The Burden: Global and Personal Perspectives

Professor Julián Panés

The global burden of UC is considerable and continues to rise, even in western countries where historical prevalence was already high.[1] The natural history of UC suggests that in the years following diagnosis, only half of all patients achieve remission, with the remainder continuing to experience disease burden; this results in an increasing proportion requiring colectomy. After 10 years of treatment,

over one-third of patients still have active disease and 20% will undergo colectomy.[2]

Even for patients who initially present with a limited extent of disease, such as those with proctitis or proctosigmoiditis, UC will progress to a greater extent of disease extension in about one-third of patients, with 10–20% developing extensive colitis.[3]

A case–control study by Etchevers et al.[4] suggests that UC acquires a particularly severe and refractory course when disease extension occurs. Inflammatory markers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate, are higher in progressing patients compared with patients with extensive but stable disease. Pharmacological and inpatient requirements are greater, and the number needing surgical intervention increased from 5% to 19%. In paediatric patients, the situation is even more concerning: approximately 10% of adult patients have experienced colectomy within 10 years of diagnosis,[5] while 20% of children have undergone colectomy after only 5 years.[6]

The patient perception of disease burden was investigated by the IMPACT study, an online survey of inflammatory bowel disease (IBD) patients conducted by the European Patient Association, with almost 5,000 patients (63% with Crohn's disease [CD], 33% with UC) from 24 countries participating.[7] Results suggest that the impact of disease on everyday working behaviour is similar between UC and CD patients. Almost two-thirds of patients feel stressed or pressured about 'sick leave', whilst 30% consider themselves quieter at meetings. Participation in social activities and general motivation is reduced compared with their colleagues, and irritability is increased.[7] In terms of quality of life, over half of patients consider that UC 'controls their lives', a greater proportion than reported for patients with asthma or rheumatoid arthritis,[8] with even mild symptoms having an impact on Inflammatory Bowel Disease Questionnaire (IBDQ) scores.[9]

Direct assessment of UC disease burden will be measured in the international, 2-year observational ICONIC study, which will use a variety of instruments to measure the multi-faceted burden of disease in recently diagnosed UC patients. The ICONIC study will recruit 1,800 patients and will use the innovative Pictorial Representation of Illness and Self Measure (PRISM) tool to define individual disease burden[10] and highlight any differences in perception of disease burden between patients and physicians.

In patients undergoing surgery, colectomy does not necessarily lead to a restoration of 'normal life'. One-third of patients experience postoperative complications, with approximately 11–44% reporting short-term complications (e.g. infections or pouch-related) and 19–55% reporting long-term complications (e.g. pouchitis, CD of the pouch, infertility, faecal incontinence). The psychological burden of procedure-associated infertility should not be underestimated.[11]

Recognising the burden of UC is key to understanding the need for intervention, either medical or surgical. However, the impact of current and appropriate treatment on disease burden and progression should be considered carefully. When assessing the risk of developing colon cancer in patients with IBD, data suggest that UC patients still have an elevated incidence compared with the general population. However, the risk of colon cancer is not greater than the general population for CD patients.[12]

A recent investigation of a Danish patient cohort (n=35,782) suggests that UC patients have experienced a progressive and significant decline in the cumulative probability of colectomy over time: a reduction of almost 50% since 1979–1986.[13] However, findings from a separate study analysing the rate of colectomy between 1998 and 2011 suggest that the rate has not changed over the last 20 years.[14]

Whilst contradictory, it is important to note that even recent, well-designed studies do not investigate whether there have been changes in the time from diagnosis to surgery, or if there is a delay in the time from diagnosis to initiation of immunomodulators (IMMs) or biological therapies (which could be identified by evaluating cumulative exposure to corticosteroids). Therefore, it is hard to determine if appropriate therapies, initiated earlier, might be able to alter the disease course.

Suggestions that IMMs and biological therapies are introduced too late are based on comparisons between UC and CD. In patients with CD, where IMMs and biological therapies are used more extensively and are initiated earlier in the course of disease, there have been marked reductions in the rates of surgery. This finding is not observed in UC patients, where penetration of these drugs is lower and initiation is later in the disease course (Figure 1).[15]

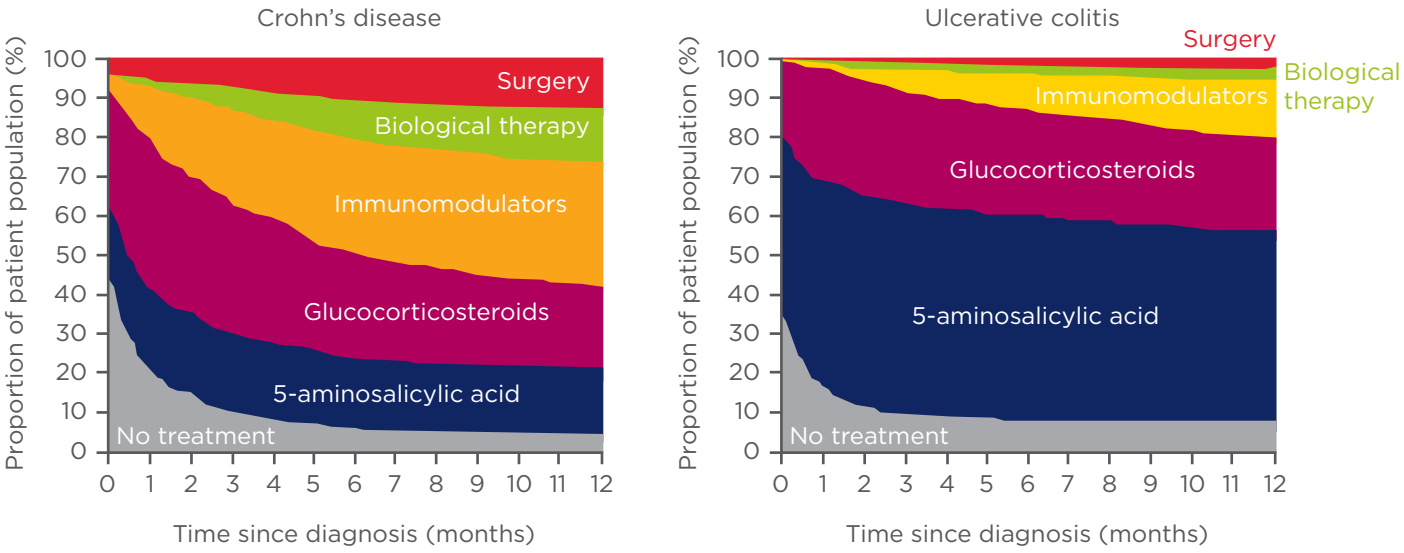

Figure 1: Change in treatment strategy with earlier and more frequent use of immunomodulators and biologicals in Crohn's disease has been associated with reduced surgery rates.[15]

While it is often considered less serious than CD, UC is increasingly recognised as a disease that has a major impact on patient quality of life. Understanding patient issues is important, as is awareness of the impact of symptoms both during and between the flares, to establish meaningful patient-centred management goals and treat each patient appropriately and effectively.

The Patient: Aligning Clinical Management with Patient Needs

Professor Edouard Louis

Patient satisfaction with their IBD care is lower than expected. Only half of patients consider the IBD care that they receive to be 'excellent' or 'very good',[16] and a perception gap exists between clinicians and patients over the impact of UC on everyday life. While most clinicians may consider that patients have symptomatic control, the majority of patients consider their symptoms to be incompletely controlled and causing them difficulties in daily life.[17] Furthermore, when investigating which symptoms are most bothersome, there are discrepancies between healthcare providers and patients. While urgency, number of stools, and blood in stools are concerning for both patients and clinicians, physicians and nurses underestimate the impact of pain and pill burden on patients.[18]

The levels of acceptable risk for a specific clinical outcome can also vary between clinician and patient. Clinicians may consider that patients would accept a relatively high risk of infection, progressive multifocal leukoencephalopathy, or lymphoma to reduce disease severity from severe to moderate levels, whereas patients are willing to accept the most risk for moderate disease going into remission.[19]

Although verbalised differently, the main treatment goals of patients and clinicians are similar: clinicians focus on induction of remission, maintaining steroid-free remission, and preventing complications, while patients focus on fast symptom relief, sustained symptom control with minimal side effects, and avoiding hospitalisation and surgery.

Recognising shared goals facilitates discussion regarding treatment plans focussed on addressing these requirements. The CYSIF study demonstrated that fast symptom relief in the presence of acute severe colitis is possible with use of infliximab or ciclosporin.[20] With moderate-to-severe disease, anti-tumour necrosis factor agents (anti-TNFs), such as subcutaneous adalimumab, provide significant decreases in stool frequency and incidence of blood in stools within 2 weeks of treatment initiation;[21,22] these symptoms are important to patients and translate into improvement in Mayo score responses for the clinician.[21]

The ULTRA studies of adalimumab demonstrate that sustained symptom relief with minimal side

effects is a realistic treatment goal. Remission and mucosal healing rates were achieved early (data showed this from Week 8) and maintained through 4 years of treatment. In addition, in patients who used corticosteroids at baseline, the proportion of patients who discontinued corticosteroids increased over time from Week 16 to Week 208 of adalimumab treatment.[23]

The tolerability profiles for biologics are well characterised and major side effects are rare. When considering adalimumab, analysis of all adult UC clinical trials, comprising over 3,000 patient-years of follow-up, demonstrates reassuring safety outcomes with no increase in mortality rates compared with the general population. Side effects of particular concern for patients, such as serious infections, malignancy, and demyelinating disorders, have event rates per 100 patient-years that are quite low: 3.4, 0.9, and <0.1, respectively.[24]

In terms of avoiding complications such as hospitalisation and surgery, a recent meta-analysis evaluating infliximab and adalimumab studies determined that both of these treatments demonstrate reductions in the risk of hospitalisation in UC patients compared with placebo, with a significant favourable overall treatment effect (risk ratio [RR]: 0.71, 95% confidence interval [CI]: 0.56–0.90; p=0.004).[25]

The ability to understand patient concerns and offer appropriate, effective treatment enables clinicians and patients to work together towards improving outcomes. However, it is critical to understand and discuss the concerns of the patient, especially as patient belief in their therapy is a key aspect of long-term treatment adherence and disease management. This is particularly true in chronic treatment, where necessity beliefs (personal judgement on the need for medication) may decrease and concerns about potential side effects may increase, thus potentially increasing the risk of noncompliance.[26]

The ALIGN study was designed to assess the correlation between patients' necessity beliefs and concerns regarding their therapies with long-term treatment adherence. Overall results from ALIGN indicate that UC patients have similar concerns regarding anti-TNFs and IMMs, both of which are greater than those for 5-aminosalicylic acid (5-ASA). However, they believe that anti-TNF agents are more necessary to control their disease than either 5-ASAs or IMMs. Therefore, although patients may have some concerns about anti-TNF therapy, their belief that it is necessary to control their disease outweighs their concerns, resulting in high medication adherence.[27]

The next step in engaging patients regarding their care is complete involvement in the disease management process. In a study performed in Denmark and Ireland, UC patients (n=333) were randomised to receive treatment with either 'standard care' or a web-based interaction with the clinical team to permit self-treatment. After 12 months, 88% of patients preferred web-based management, and adherence to 4 weeks of acute treatment increased by 30–40%, compared with standard care. In addition, patients receiving web-based management had reductions in the median duration of relapse: 18 days (95% CI: 10–21) in the web-based management group compared with 77 days (95% CI: 46–108) in the standard care group. There were also fewer medical visits associated with web-based patients, with cost savings estimated at €189/patient/year.[28]

Disease burden in UC is often underestimated and sometimes misinterpreted by clinicians. Nonetheless, healthcare providers and patients often have similar treatment goals and therefore a structured collaboration between patients and clinicians may help to improve therapeutic adherence and overall IBD management.

The Treatment: Optimising Strategies to Improve Outcomes

Professor Paul Rutgeerts

Treatment goals for patients include complete resolution of symptoms with limited or manageable side effects and a normalised quality of life. From the perspective of the clinician, disease remission (especially with mucosal healing), eliminating steroids from the therapeutic regimen, and avoiding therapy escalation are key for long-term management. Improved outcomes result in fewer complications, hospitalisations, and surgeries, and lower mortality, thus decreasing societal and financial costs.

Current issues in the treatment of UC include early identification of patients with predicted poor outcome, use of appropriate therapies earlier in the disease course, and optimising such therapies to improve patient outcomes. Such issues may provide

opportunities to implement top-down management approaches in UC patients.

Identifying aggressive disease is complex in patients with UC, but may be associated with young age at presentation, a requirement for steroids as part of initial therapy, extent of disease at time of treatment, and extension of disease course over time. Biological signs of inflammation are also important in predicting aggressive disease, with mucosal ulceration[29] and high CRP[30] as signatures of severe and aggressive outcomes.

UC appears to be a progressive disease. In long-term UC, chronic inflammation can lead to epithelial fibrosis and 'lead pipe' colon,[31] resulting in colon shortening and chronic watery diarrhoea, with associated difficulties for patient continence.[32] The long-term duration of disease may also result in development of dysplasia, the precursor to colonic cancer; the incidence of colon cancer is reported as 18% at 30 years.[33] Finally, regeneration of mucosa characteristic of UC leads to extensive pseudopolyps, which hinder surveillance.[32]

UC patients may be categorised into four groups: (1) patients responding to 5-ASAs or steroids with sustained remission or occasional flares; (2) patients with chronically active disease who are never completely controlled on 'standard' therapies (including steroid-dependent or refractory patients); (3) patients with acute severe UC; and (4) candidates for colectomy. Patients responding to 5-ASAs or steroids with sustained remission have a favourable prognosis and are straightforward to manage with appropriate therapies. In the presence of occasional flares, use of oral or topical steroids should be considered and maintenance therapy can remain unchanged (Figure 2). Patients experiencing more than one flare per year require a reassessment of treatment.

Chronic active disease is never completely controlled with conventional therapy. However, there is often a disconnect between the perceptions of clinicians and patients in this category. While the clinician considers the patient to be adequately managed, there is an inadequate or incomplete response to conventional therapy. The patient is functioning and non-hospitalised, but is under-treated and has persistent symptoms with an ongoing impact on daily quality of life; ineffective low doses of steroid are often still included in the treatment regimen. Such patients require a change in therapy as IMMs are ineffective. For patients with more challenging steroid-dependent or refractory disease, anti-TNF and azathioprine combination therapy (or anti-migration therapy) should be initiated early (Figure 2); oral 5-ASAs could potentially be stopped. The goal of treatment should be mucosal healing, which significantly reduces rates of colectomy at 1 year compared with patients with inflammatory activity: 19% versus 81%, respectively (RR: 0.22, 95% CI: 0.06–0.79; p=0.02).[34]

Patients with acute severe colitis are key candidates for top-down therapy, which provides a reduced time to disease remission and mucosal healing with the potential benefits of steroid and immunosuppressant avoidance. Other patient categories may also benefit from top-down approaches. Patients with extensive colitis and CRP elevation who demonstrate resistance to optimal-dose 5-ASA treatment should be considered, as should those with persistent, even low-grade, active inflammation despite conventional therapy. With the decreasing costs and an extensive range of anti-TNF therapies and anti-migration therapies, maintained remission and the avoidance of dysplasia and surgery enable improved management as treatment approaches become more cost-effective.

Optimisation of therapies can improve patient outcomes. The UC SUCCESS study demonstrates that combination therapy with infliximab and azathioprine significantly increases both clinical remission rates and mucosal healing after 16 weeks compared with either treatment alone. Mucosal healing results are reported as 37% for azathioprine, 55% for infliximab monotherapy, and 63% for combination therapy.[35]

There is an apparent correlation between therapeutic concentration and remission rates. This can be seen for adalimumab, where UC or CD patients with lower serum concentrations are less likely to achieve remission;[36] lower trough levels are also associated with reduced mucosal healing rates.[37] Investigation of serum level optimisation in the TAXIT infliximab study (n=260) suggests that, following stable clinical and biological remission at 1 year, only 43% of patients had optimal infliximab trough levels (3–7 µg/mL). In total, 26% of patients had infliximab trough levels >7 µg/mL, 22% had low levels (<3 µg/mL), and 9% had undetectable trough levels; most of these patients also had anti-infliximab antibodies.[38]

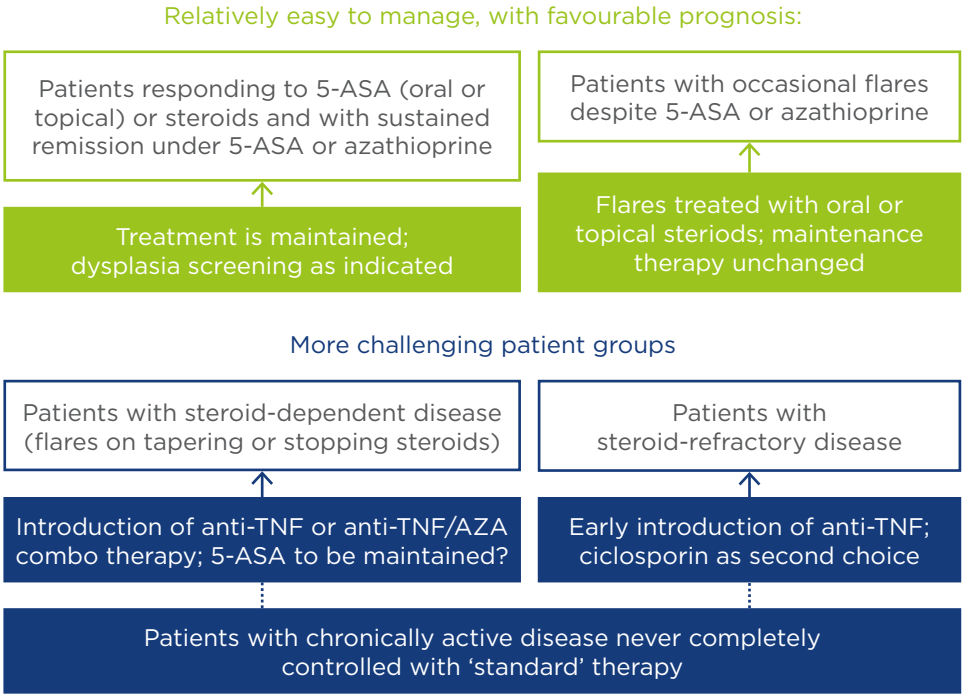

Figure 2: Selection of therapy in the clinical practice of Professor Paul Rutgeerts.
5-ASA: 5-aminosalicylic acid; anti-TNF: anti-tumour necrosis factor; AZA: azathioprine.

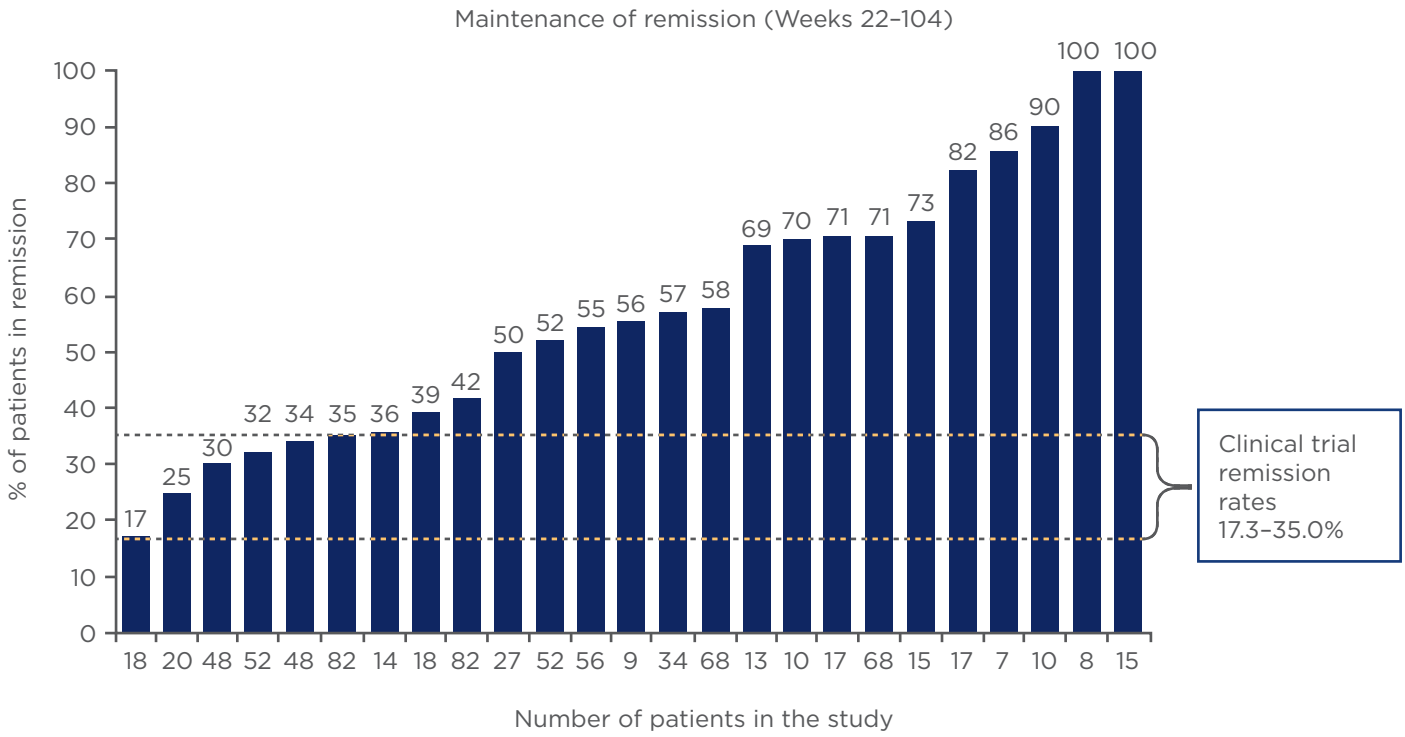

Figure 3: Anti-TNFs: real-world effectiveness.[40-50]
Anti-TNF: anti-tumour necrosis factor.

The ongoing SERENE UC study will investigate the efficacy of a higher adalimumab induction dosing strategy to induce clinical remission, and evaluates different maintenance dosing strategies, including therapeutic drug monitoring, to determine the optimal dosing required to maintain remission through 1 year.[39]

There is an important gap between results from clinical trials and real-world clinical practice.

Compared with controlled clinical trials, patients in clinical practice are more heterogeneous and physicians are able to exercise variable treatment regimens, including dose optimisation, to obtain maximal clinical benefit. Maintenance of remission rates in clinical trials of anti-TNF agents range from 17–35%. In contrast, most real-world cohorts report remission rates higher than those observed in clinical trials (Figure 3).[40-50]

Conventional step-up care has not altered the natural history of IBD. To reduce the burden of UC in clinical practice, management goals should be set in collaboration with the patient, who is categorised according to disease characteristics and prognosis. To optimise outcomes, effective therapies must be implemented early in the disease course in high-risk patients, who should be considered for top-down management. There should be a time-bound, monitored approach to reach treatment goals, and all therapeutic decisions must be made within the context of a full benefit/risk assessment.

Conclusion

UC has a major impact on quality of life, and clinicians need to fully understand the issues most important to patients. As part of a patient-centric approach, close collaboration is required to identify meaningful management goals and optimise treatment outcomes. Clinical management approaches should categorise patients according to disease characteristics and prognosis, and initiate early, effective treatment in high-risk patients.

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GUT MICROBIOTA: MODULATE ITS COMPLEXITY TO RESTORE THE BALANCE

This symposium took place on 26th October 2015 as part of the 23rd United European Gastroenterology Week in Barcelona, Spain

Chairperson

Fermín Mearin[1]

Speakers

Fermín Mearin,[1] Antonio Gasbarrini,[2] Peter Malfertheiner,[3] Mark Pimentel[4]

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MEETING SUMMARY

The importance of the gut microbiota to health is becoming more widely appreciated. The range of commensal microorganisms in healthy individuals and in patients with a variety of digestive diseases is under active investigation, and evidence is accumulating to suggest that both the diversity and balance of bacterial species are important for health. Disturbance of the balance of microorganisms – dysbiosis – is associated with obesity and a variety of diseases. Restoring the balance by modulating the microbiota through diet, probiotics, or drugs is now being developed as a potential treatment for digestive diseases. Rifaximin has been shown to increase levels of beneficial bacterial species without perturbing the overall composition of the microbiota in patients with a variety of digestive diseases, making it a 'eubiotic' rather than an antibiotic. Rifaximin has demonstrated clinical benefit in the treatment of symptomatic uncomplicated diverticular disease, where changes in the colonic microbiota contribute to the pathogenesis of this disease. Modulating the microbiota is also a promising treatment for some types of irritable bowel syndrome (IBS) that have been linked to an overgrowth of coliform and *Aeromonas* species in the small intestine. Rifaximin has demonstrated efficacy in relieving symptoms and reducing relapses in diarrhoeal IBS in the TARGET-1, 2, and 3 trials, without reducing microbial diversity or increasing antimicrobial resistance. While many aspects of the balance of gut microbiota in disease are not yet fully understood, the new understanding of rifaximin as a modulator of gut microbiota may open up new treatment options in digestive disease.

Introduction

Professor Fermín Mearin

Although the hypothesis that human beings can live in symbiosis with some bacteria dates back over a century, the idea that the gut microbiota might play a beneficial role in the health of the host has only recently arisen. The human gut is home to trillions of commensal bacteria, some of which may be beneficial and some of which may be harmful.

It is becoming apparent that both a diversity of bacterial types and a balance of different bacterial species are necessary for health. Modulating the complexity of the gut microbiota to restore the balance of bacterial species is a promising approach for treating gut diseases.

Composition and Function of the Fourth Organ of the Gastrointestinal Tract

Professor Antonio Gasbarrini

The gut microbiota, comprising a 95% gene identity of 9 phyla, over 1,000 species, and more than 15,000 strains, can be considered a metabolic organ – the gut metabolome rather than the gut microbiome. The gut microbiota consists mainly of bacteria. Firmicutes and Bacteroidetes constitute the majority of present phyla,[1] alongside characteristic viruses and yeasts,[2,3] and sometimes protozoa (e.g. helminths and other parasites). Many of these commensal organisms are either beneficial or harmless, while others can be harmful.[3,4] The variety of microorganisms within a person's gut, known as their enterotype, is unique to the individual, and is determined by many life events from birth onwards.[5,6] Factors that influence enterotype include: whether one is bottle or breast-fed and the types of solid food consumed as an infant, antibiotic treatments, malnutrition as a toddler, obesity as an adult, and old age.[6] The commensal gut microbiota contributes to gastrointestinal (GI) homeostasis in several ways. For example, the gut microbiota contributes to the barrier function of the intestinal lining,[7] although the mucus of the intestinal lining is the main constituent.[8,9] More importantly, the gut microbiota plays a role in the education of the innate and acquired immune systems.[10] In addition, the metabolic effects of the gut microbiota are considerable – without it, it would not be possible to metabolise the complex polysaccharides of dietary fibre.[11,12] The precise balance of the gut microbiota can influence persisting metabolic traits, and evidence from animal models suggests that the overgrowth of certain strains of gut bacteria may have a causal role in obesity.[13-15]

Maintaining the balance of gut bacteria species (eubiosis) is important for health. For instance, *Clostridium difficile*, especially toxin-producing species, remain in spore form in the gut due to the actions of *Clostridium scindens* on bile acids.

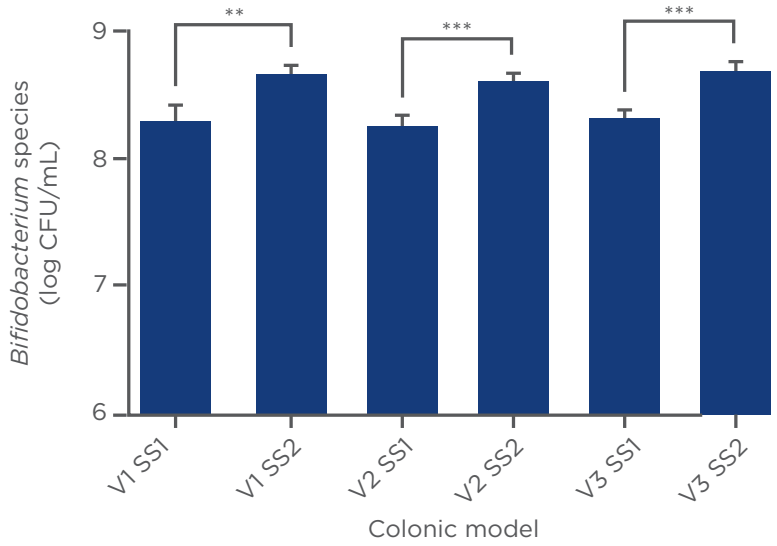

Figure 1: Rifaximin treatment increases the abundance of *Bifidobacterium* species in faecal microbiota of Crohn's disease patients.

Bifidobacteria detected by fluorescent *in situ* hybridisation in culture broths recovered from three different culture vessels (V1, V2, and V3) in an *in vitro* colonic model system before (SS1) and after (SS2) rifaximin treatment. Results are reported as the means of data of four colonic models ± standard error of mean. For each colonic model, measurements were performed in triplicate.

**p<0.01; ***p<0.001.

CFU: colony forming unit.

Beta-lactam antibiotics kill *C. scindens*, which may allow *C. difficile* to become vegetative and potentially toxic. Dysbiosis – the failure of the host–microbiota balance – and breakdown of the gut barrier are implicated in a variety of digestive diseases, such as irritable bowel syndrome (IBS) or diverticular disease. The modulation of the gut microbiota is therefore a promising target for treating these diseases. The balance of gut microbiota can be modulated by diet, by correcting predisposing conditions, or with antibiotics. Whereas systemic antibiotics, such as vancomycin, may kill beneficial commensal bacterial species as well as pathogenic species,[16] gut-specific topical, non-absorbable antibiotics, such as rifaximin, can have a beneficial effect on the overall balance of the gut microbiota.[17,18]

Rifaximin does not have a traditional antibiotic effect, but acts through inhibition of bacterial adherence to the gut mucosa.[17] Animal models suggested potential eubiotic effects of rifaximin favourably affecting the balance of gut bacteria, primarily by increasing *Bifidobacterium* (Figure 1), *Faecalibacterium prausnitzii*, and lactobacilli, without perturbing the overall composition of the microbiota.[19-22] Despite these promising experimental findings, it was not known if the eubiotic effects of rifaximin would translate into humans. A recent observational prospective study sought to answer this question in patients with a variety of digestive diseases, including ulcerative colitis, Crohn's disease, IBS, diverticular disease, and liver cirrhosis with hepatic encephalopathy. Patients were treated with 1,200 mg of rifaximin per day over a 10-day period. Levels of gut microbiota were measured at baseline, after the 10-day treatment period, and 1 month later. Principal coordinate analysis demonstrated that rifaximin did not change the overall composition of the gut microbiota. However, differential abundance analysis revealed a significant increase in lactobacilli at the end of treatment, which persisted 1 month after treatment ($p<0.0001$).[23]

It is thought that the increase in lactobacilli may mediate the anti-inflammatory effects of rifaximin.[24,25] Rifaximin may thus be viewed as a 'eubiotic' rather than an 'antibiotic', and is an important contribution to the armamentarium for modulating the microbiota to treat digestive diseases.

Microbiota Modulation in Diverticular Disease

Professor Peter Malfertheiner

Diverticulae in the colon are highly prevalent and age-dependent.[26] They are an important cause of morbidity and a significant health economic burden.[27,28] Diverticulae occur when the mucosal and submucosal gut lining extrovert through the muscular intestinal wall, generally at sites where the vascular system penetrates. The formation of faecaliths in the diverticulae can lead to inflammation and diverticulitis with potential complications, such as perforation, bleeding, stenosis, and fistula.[26] The majority (80%) of patients with diverticulae are asymptomatic and the remaining 20% of symptomatic patients have chronic relapsing symptoms, recently defined as symptomatic uncomplicated diverticular disease (SUDD), or may develop diverticulitis with or without complications such as bleeding (Figure 2).

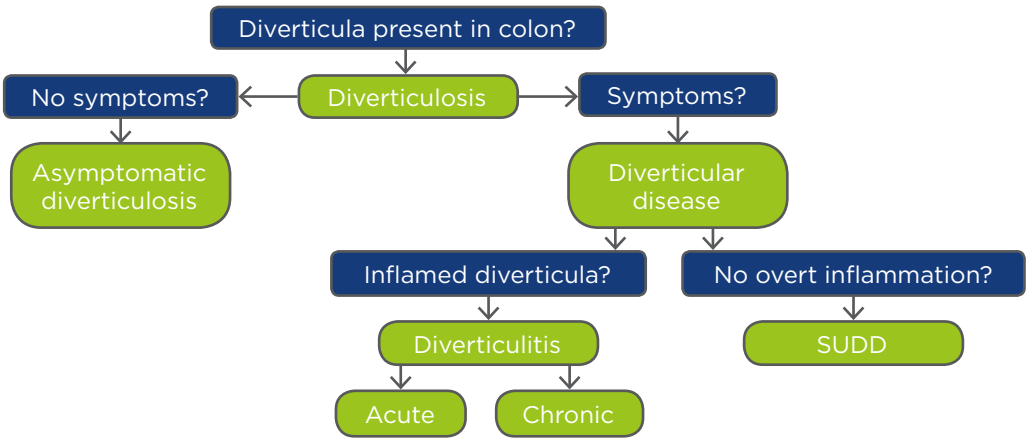

Figure 2: Proposed taxonomy of diverticular-related terms – basis for therapeutic decisions.[26]
SUDD: symptomatic uncomplicated diverticular disease.

Patients with SUDD are at an increased risk of developing acute diverticulitis.

Dysbiosis of gut bacteria has been linked to SUDD and diverticulitis.[29] This appreciation of the role of gut microbiota in diverticular disease has influenced treatment, following demonstrations that systemic antibiotics are not necessary to treat acute non-complicated diverticulitis.[30-32] SUDD is thought to develop from the weakening of the colonic wall and degenerative changes in the enteric nerves, combined with changes in the colonic microbiota and an inflammatory response. There are similarities between the symptoms of SUDD and IBS, and it has been proposed that left lower quadrant pain for >24 hours combined with increased faecal calprotectin should characterise SUDD.[33]

Treatment of SUDD aims to decrease symptom intensity and prevent the recurrence of acute diverticulitis by targeting the pathophysiological mechanisms of the disease.[26] As well as affecting the gut microbiota, fibre acts to normalise colon motility, and has a level 1 recommendation from the National Diverticula Study Group.[34] Although a clinical benefit has been demonstrated for 5-aminosalicylic acid drugs in the treatment of low-grade inflammation,[35,36] the PREVENT 1 and 2 trials failed to demonstrate a benefit for mesalazine over placebo in preventing relapses.[37] The gut microbiota is therefore a promising target to treat SUDD. Rifaximin has been proven to modulate the gut microbiota to beneficial effect in SUDD in several randomised trials.[38] In these trials, disease symptoms were improved and patients experienced a reduction in relapses of acute diverticulitis, with few adverse events.[39] Long-term cyclic administration of rifaximin is effective in reducing the symptoms, complications, severity, and frequency of diverticular disease. Most patients can readily benefit from symptom relief, and the number needed to treat for one patient to benefit from complete symptom relief was three, according to a recent meta-analysis.[38] However, more data are needed to better address the prevention of relapsing symptoms, as well as acute diverticulitis.

New Evidence in IBS: The Role of Gut Microbiota

Professor Mark Pimentel

Recent evidence indicates that the gut microbiota is important in IBS pathophysiology. At the same time, evidence is poor for psychological causes, such as stress. Notably, a recent study on the role of stress in the development of IBS identified only exposure to acute gastroenteritis as being associated with IBS.[40] Thus, a new hypothesis has emerged for the pathophysiology of IBS: IBS is a disease triggered, at least in part, by a change in the gut microbiota caused by gastroenteritis. The role of the gut microbiota suggests that IBS could therefore be an antibiotic-sensitive disease.

In a variety of trials, characterisation of the microbiota in patients with IBS has demonstrated changes in the gut microbiota, most notably an associated overgrowth of coliforms and *Aeromonas* species (Figure 3).[41-43]

The aforementioned hypothesis was the basis for the TARGET trials of the antibiotic rifaximin as a treatment for IBS. In TARGET 1 and 2, rifaximin not only demonstrated efficacy in symptom relief over placebo 4 weeks after treatment, but also showed a durable response 3 months after treatment.[44] It can therefore be suggested that rifaximin treats the cause of the disease rather than the symptoms alone. This contrasts with treatments such as the anti-diarrhoeal alosetron, where the benefits cease as soon as the treatment ends.[45] The TARGET 3 trial included a more stringent design to investigate the safety and efficacy of repeated use of rifaximin in patients who have had multiple relapses, and the durability of its effect. The trial had an initial open-label phase to screen out placebo responders, and a composite endpoint of simultaneous improvement of abdominal pain and stool consistency in 2 out of 4 weeks, with 18 weeks' follow-up for relapses. In the initial open-label phase, 72% of patients had an improvement in at least one component of the composite endpoint. Of the patients who met the composite outcome in the open-label phase, more than 1 out of 3 (35%) did not have a relapse of symptoms in the following 6 months. Those who did relapse were entered in the main double-blind phase of the trial.[46] Significantly more patients treated with rifaximin were responders in the first repeat treatment phase compared with the placebo group, which was a consistent treatment effect. Notably, patients did not return to baseline symptom severity after treatment with rifaximin.[46] TARGET 3 was the largest deep sequencing trial to date, and showed that rifaximin did not alter 98% of the organisms in the gut or the stool. Furthermore, microbial resistance did not change in the remaining organisms.[46]

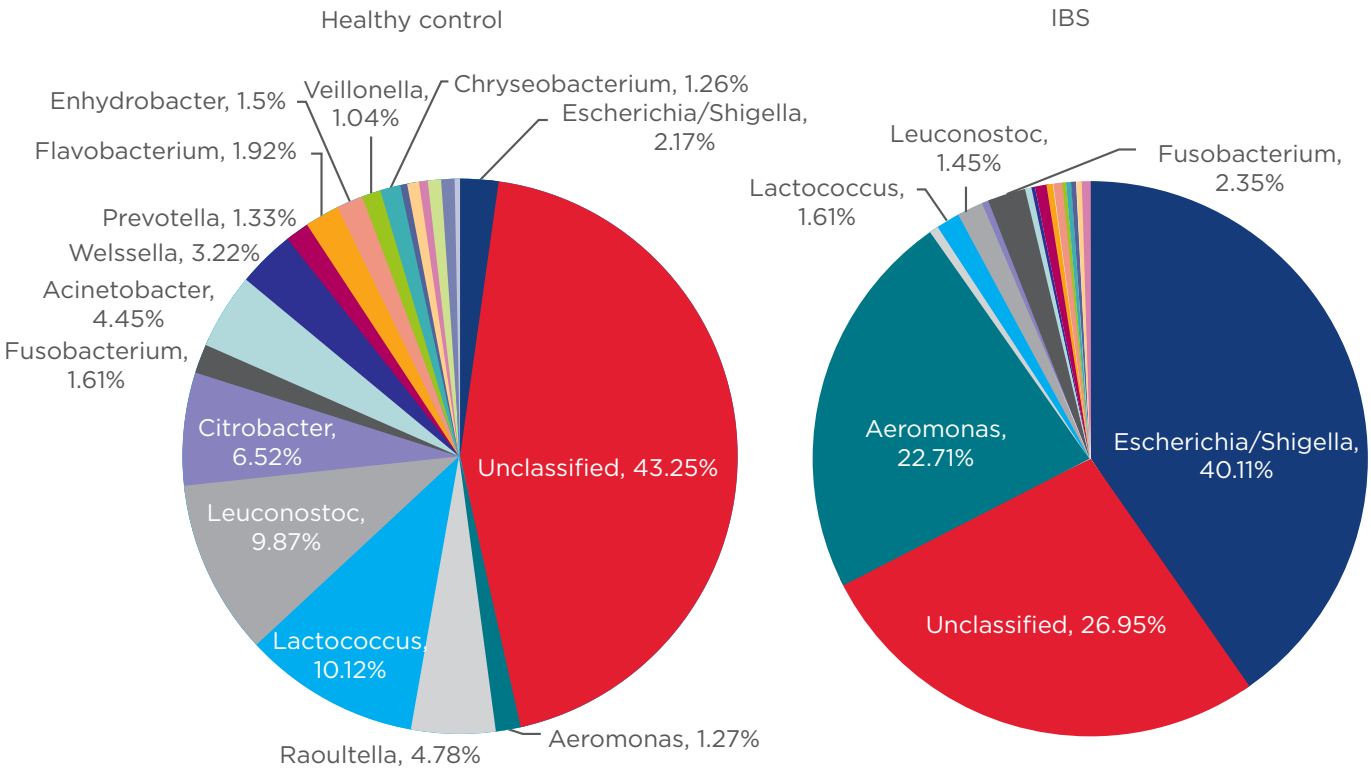

Figure 3: Microbial distribution on 16S amplicon sequencing in IBS patients and healthy controls demonstrates reduced gut microbiome diversity in IBS patients.[41]

The charts show the average relative abundance of bacterial genera identified in five irritable bowel syndrome (IBS) patients and five controls; genera with a relative abundance >1% are labelled by name.

The efficacy of rifaximin in IBS may be linked to the hypothesis that perturbations of gut microbiota contributes to the development of IBS. Studies have shown that acute gastroenteritis increases the risk of developing IBS.[47,48] An animal model of post-infectious IBS following *Campylobacter* infection tested the hypothesis that cytolethal distending toxin B (CdtB) was the toxin involved in development of IBS following gastroenteritis, and showed that *Campylobacter* strains lacking CdtB did not induce IBS.[49] Antibodies to CdtB were found to cross-react with vinculin. Blood tests for antibodies to CdtB and vinculin in patients from the TARGET 3 trial and in patients with other gut disorders were able to identify IBS patients;[50] this supports the hypothesised pathological sequence.

At least one subset of IBS has shown to be an organic disease because small intestine bacterial changes are seen in at least 60% of IBS patients, and diarrhoeal IBS can be effectively treated with the microbiome-balancing therapy rifaximin. Gastroenteritis is involved in the development of IBS, most likely through autoimmunity to vinculin triggered by immune responses to CdtB, and serum anti-CdtB and anti-vinculin can distinguish IBS from inflammatory bowel disease.

Conclusion

Many aspects of the balance of gut microbiota in disease are yet to be clarified, and improvements in the understanding of how rifaximin acts on the balance of microbiota in GI diseases are anticipated. The new definition of rifaximin as a modulator of gut microbiota may open up potential new indications for this therapy.

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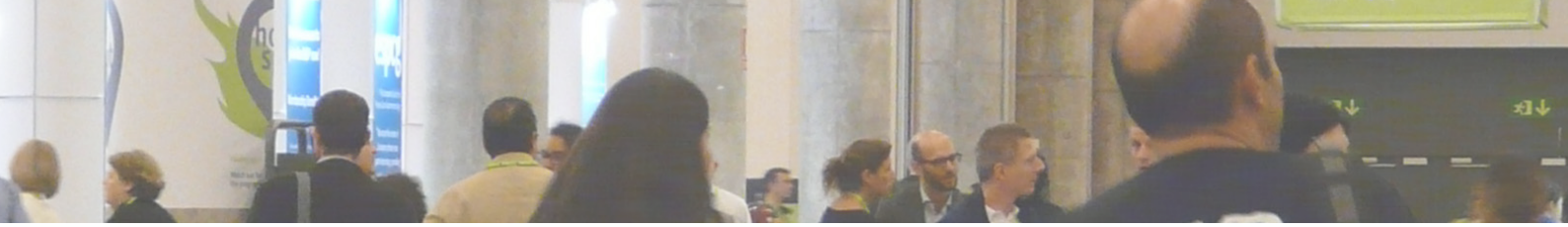
AWARD WINNERS AT UEG WEEK 2015

Every year, the organisers of UEG Week award five of the research abstracts submitted to the congress a Top Abstract Prize and €10,000 in recognition of their achievements, and to aid the lead authors' ongoing research. The five Top Abstract Prizes at UEG Week 2015 were received by delegates from the Netherlands, Germany, and the USA, with two awarded to delegates from the UK. Three of the abstracts focussed on clinical research, while the remaining two addressed preclinical topics.

A Top Abstract Prize was awarded to William J. Sandborn (USA) for his description of the safety and efficacy results from the maintenance period of the Phase II TOUCHSTONE trial of ozanimod – a selective oral sphingosine 1-phosphate 1 and 5 receptor modulator, in ulcerative colitis (UC). The study results showed that patients with moderate-to-severe UC who continued treatment with ozanimod past Week 8 were more likely to achieve and maintain clinical remission, clinical response, and mucosal improvement compared with those receiving placebo. TOUCHSTONE included 197 patients randomised 1:1:1 to treatment with either placebo (n=65), low-dose (LD) ozanimod (n=65), or high-dose (HD) ozanimod (n=67), with the maintenance period including those patients who achieved a clinical response at Week 8 and who could continue their original treatment for a further 24 weeks. A total of 103 patients (52.3%) included in TOUCHSTONE entered the maintenance period, and 91 (88.3%) completed it. Of those receiving placebo, LD ozanimod, and HD ozanimod, respectively: clinical remission at Week 32 was achieved by 6.2%, 26.2% (p=0.0021, all p values versus placebo), and 20.9% (p=0.0108); clinical response occurred in 20.0%, 35.4% (p=0.0571), and 50.7% (p=0.0002); mucosal improvement (Mayo endo-subscore ≤1) occurred in

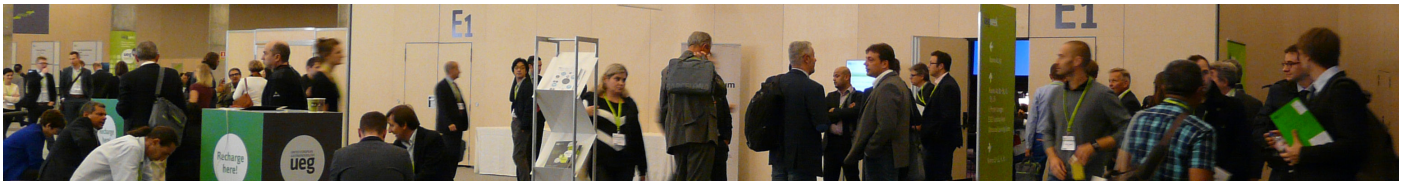


12.3%, 32.3% (p=0.0064), and 32.8% (p=0.0046); improvement in overall Mayo score from baseline to Week 32 was 1.6, 2.2 (p=0.1932), and 3.4 (p=0.0004); and adverse events (AEs) occurred in 32.0%, 11.1%, and 26.2%, with no AEs of special interest reported.

The identification of these predictive factors may allow improved assessment of the risk of neoplastic progression in BO patients and help improve surveillance strategies.

The prize awarded to Edmund Derbyshire (UK) recognised his abstract reporting results from the largest case series in Europe to include data on the incidence, management, and outcomes of colonoscopic bowel perforations. As part of the English NHS Bowel Cancer Screening Programme, a colonoscopy performed at one of the 61 bowel cancer screening centres in England is offered to all those aged 60–74 years and returning an abnormal faecal occult blood test. The programme records details of AEs following colonoscopy, with patients being contacted at least twice post-procedure and details entered into a national online database. A total of 263,129 endoscopic procedures and 147 colonoscopic perforations (rate: 0.06%) occurred from the start of the programme in 2006, to 13th March 2014, with perforation being defined as: air, luminal contents, or instrumentation outside the gastrointestinal tract. Complete data were available for 117 perforations, 69.2% of which were therapeutic. Diagnostic perforations were significantly associated with the need for surgery (risk ratio [RR]: 1.86, 95% confidence interval [CI]: 1.39–2.49; p=0.001), with a stoma formed in 26.1% of those having surgery. Male sex (RR: 2.07, 95% CI: 1.05–4.07; p=0.015) and a colorectal location in the sigmoid colon (RR: 2.56, 95% CI: 1.50–4.38; p=0.000) were significantly associated with stoma formation. Post-perforation morbidity, defined as an in-patient complication or new diagnosis following admission, occurred in 19.7% and was significantly associated with diagnostic perforation (RR: 2.70, 95% CI: 1.37–5.35; p=0.009) and surgery (RR: 38.18, 95% CI: 2.37–613.81; p=0.000). The median hospital stay was 9.5 days (range: 0–51) and 25.2% of patients were admitted to an intensive care unit; the mortality rate was 0.87%. The post-perforation morbidity rate of 19.7% and mortality rate of 0.87% compared favourably with previously reported case series.

Angela Bureo Gonzalez (Netherlands) received her prize in recognition of a study describing the identification of clinical and endoscopic factors capable of predicting neoplastic progression in patients with Barrett's oesophagus (BO). The authors conducted a prospective, multicentre, community-based cohort study of 1,003 BO patients in six community-based hospitals in the Netherlands in 2003, which was coordinated by a BO tertiary referral centre. The characteristics of the 1,003 patients included in the study were as follows: 72% male, mean age at diagnosis: 55±12 years, median length of BO: 3 cm (interquartile range [IQR]: 1–5), and median surveillance time: 7.1 years (IQR: 3.4–11.1). Overall, 5% of the patients developed high-grade dysplasia (HGD; 24/52) or oesophageal adenocarcinoma (OAC; 28/52), with a median time to progression of 7.9 years (IQR: 3.9–11.6). Factors identified as being significantly associated with neoplastic progression were the presence of low-grade dysplasia at baseline (odds ratio [OR]: 2.47, 95% CI: 1.01–5.85; p=0.038), age at baseline endoscopy (OR: 1.03, 95% CI: 1.00–1.05; p=0.029), and length of BO (OR: 1.22 per cm, 95% CI: 1.13–1.31, p<0.001). The analysis found that the annual risk of progression to HGD or OAC in this cohort of BO patients was 0.64% per patient-year. The identification of these predictive factors may allow improved assessment of the risk of neoplastic progression in BO patients and help improve surveillance strategies.



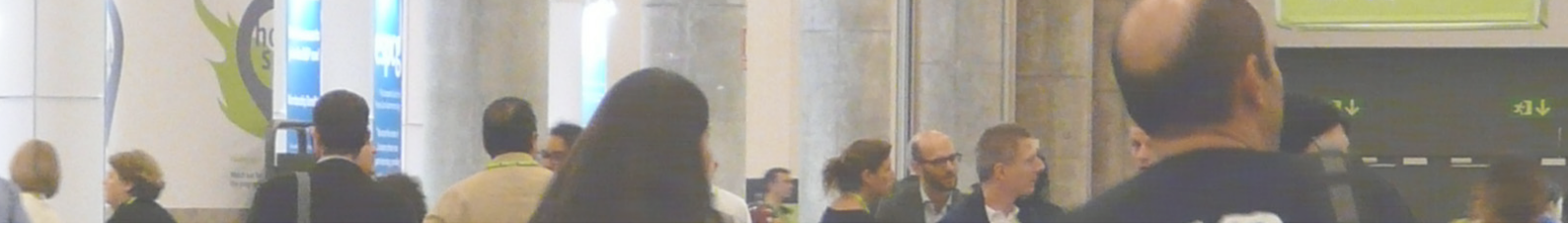
BEST ABSTRACT AWARD WINNERS

...alterations in signalling within the innate immune system may disrupt host–microbe interactions and promote an inflammatory microenvironment that favours tumourigenesis.

The second prize to be awarded for research coming from the UK was presented to Daffolyn Rachael Fels Elliott for her abstract reporting upon the identification of somatic mutations that lead to the dysregulation of Toll-like receptor (TLR) signalling in OAC. The study used whole-genome sequencing to investigate the mutational status of genes encoding TLRs in 170 OAC samples. Missense mutations in genes encoding TLRs were identified in 13.5% of the tumour samples, with mutations in the gene encoding TLR4 being most frequent (4.7%). Site-directed mutagenesis was used to prepare 10 plasmids carrying genes encoding mutant forms of TLR4 (9 containing 1 single-nucleotide variant, and 1 containing 2 single-nucleotide variants) for expression in HEK293 cells in order to assess their effects on TLR4-mediated signalling. The results showed a significant decrease in ligand-dependent signalling for seven of the nine TLR4 mutations tested; the double mutation of E439G+F703C showed an additional decrease. Three of the TLR4 mutants were subsequently expressed in the OAC cell lines OE33 and JH-EsoAd1, and specific cytokine secretion was measured following stimulation with monophosphoryl lipid A and lipopolysaccharide. Compared with cultures expressing wild-type TLR4, the concentrations of secreted interleukin (IL)-8 and IL-6 were significantly lower in cultures expressing the R787H and E439G+F703C TLR4 mutants. The E439G mutation led to no significant decrease in TLR4 signalling in the OAC cell lines following stimulation with LPS. The authors speculate that alterations in signalling within the innate immune system may disrupt host–microbe interactions and promote an inflammatory microenvironment that favours tumourigenesis.

There were no relevant differences between the genotypes, with both reaching similar efficiencies of definitive endoderm, pancreatic endoderm, and exocrine/ductal cells.

Preclinical research was also reported in the prize-winning abstract submitted by Alexander Kleger (Germany), who created an *in vitro* model of pancreatic differentiation using induced pluripotent stem (iPS) cells obtained from hair keratinocytes plucked from healthy volunteers and patients with cystic fibrosis (CF). Using their model, the researchers were able to provide evidence against the hypothesis that CF patients have defects in



pancreatic development, and were able to create a CF phenotype within a novel culture system capable of providing a patient and pancreas-specific platform for drug screening studies. The researchers generated iPS cells from hair keratinocytes and developed a stepwise differentiation protocol to recapitulate pancreatic exocrine and ductal commitment *in vitro*. They subsequently cultured these progenitors to form three-dimensional organoids that could survive more than six passages. By generating organoids from the CF transmembrane conductance regulator (CFTR)-mutated and control iPS cells, they were able to compare the stepwise pancreatic commitment capacity of each genotype. There were no relevant differences between the genotypes, with both reaching similar efficiencies of definitive endoderm, pancreatic endoderm, and exocrine/ductal cells. While CFTR-mutated exocrine cultures appeared less robust but still able to form pancreatic organoids, functional CFTR activation revealed a dramatic difference: treatment with forskolin, an established CFTR activator, led to a rapid and pronounced swelling in wild-type cultures, but led to no relevant reaction in CFTR-mutated organoids.

GENETIC POLYMORPHISMS IN TLR4-RELATED GENES PREDICT LONG-TERM EFFECT OF INFLIXIMAB IN CROHN'S DISEASE

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Crohn's disease (CD) is characterised by chronic granulomatous inflammatory changes in the gastrointestinal tract, and undergoes cycles of remission and relapse. Among the medical therapies for CD, steroids and/or anti-tumour necrosis factor (TNF)-α antibodies, such as infliximab (IFX) and adalimumab, are used in CD patients with moderate or severe disease. Although IFX is widely available for CD treatment, some primary failure patients have been unable to achieve remission at the short-term period of 10 weeks. However, some non-responders at 10 weeks did achieve remission at the long-term period of 1 year after IFX administration. Therefore, in order to identify genes related to the response to IFX, and biomarkers in order to predict the IFX therapeutic effect, we carried out a candidate gene-based association study.

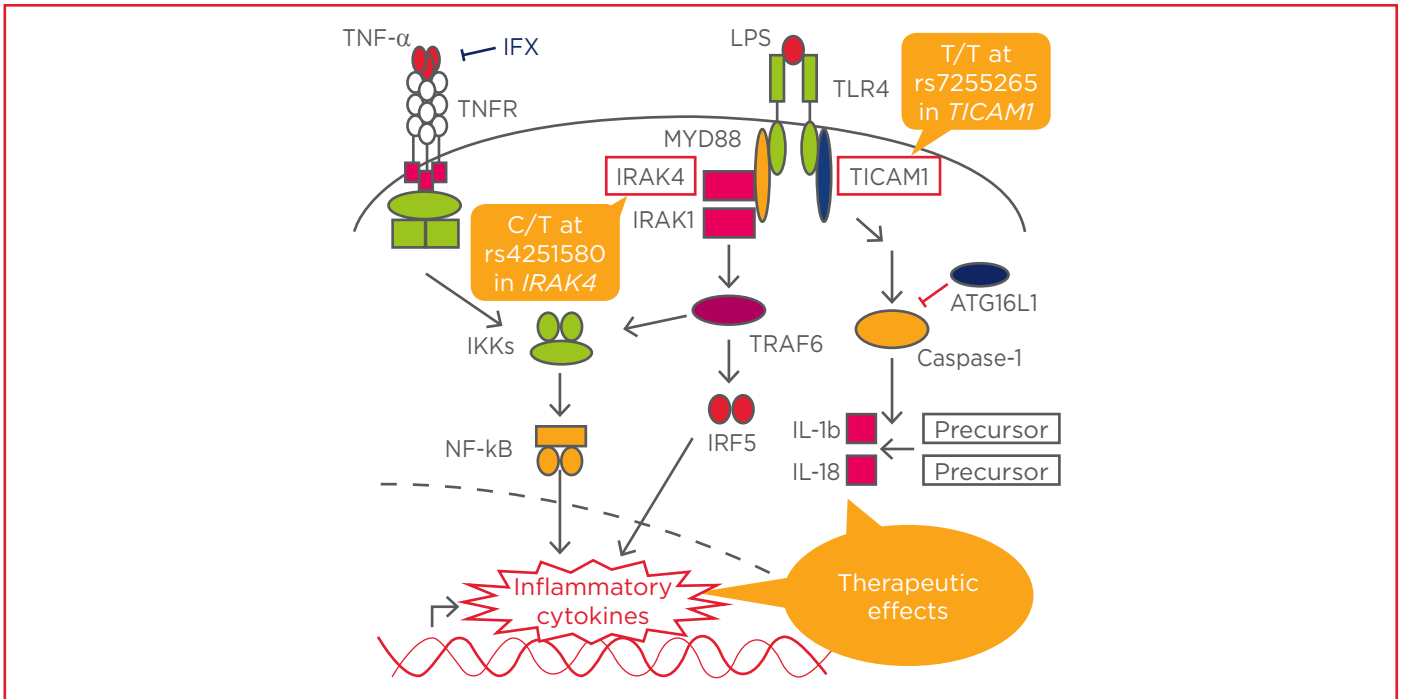

Figure 1: Intracellular signalling via TNFR and TLR4.
ATG16L1: autophagy-related 16-like 1; IFX: infliximab; IKK: IκB kinase; IL: interleukin; IRAK: interleukin 1 receptor-associated kinase; IRF5: interferon regulatory factor 5; LPS: lipopolysaccharide; MYD88: myeloid differentiation primary response gene; NF-κB: nuclear factor κB; TICAM1: Toll-like receptor adaptor molecule 1; TLR4: Toll-like receptor 4; TNF-α: tumour necrosis factor alpha; TNFR: tumour necrosis factor receptor; TRAF6: tumour necrosis factor receptor-associated factor 6.

Table 1: Effect of single-nucleotide polymorphisms (SNPs) on response to infliximab treatment in patients with Crohn's disease.

Gene	SNP	Genotype	Number of Crohn's disease patients (%)			Comparison	
			Responders (n=97)	Non-responders (n=19)		Odds ratio (95% confidence interval)	p value
TICAM1	rs7255265	C/C	42 (43.3)	7 (36.8)	Allele	0.594 (0.293–1.204)	0.146
		C/T	47 (48.5)	7 (36.8)	Dominant	0.764 (0.277–2.108)	0.602
		T/T	8 (8.2)	5 (26.3)	Recessive	0.252 (0.072–0.880)	0.038
IRAK4	rs4251580	C/C	77 (79.4)	10 (52.6)	Allele	0.370 (0.154–0.893)	0.023
		C/T	20 (20.6)	9 (47.4)	Dominant	0.289 (0.103–0.805)	0.014
		T/T	0 (0)	0 (0)	Recessive	–	–

We focussed on six target genes in the Toll-like receptor (TLR4) signalling pathway because this pathway shares downstream intracellular signal transduction molecules, such as NF-κB, with the TNF receptor signalling pathway (Figure 1).

A total of 127 unrelated CD patients were classified into two groups, responders and non-responders, based on the presence of IFX effect at 10 weeks and 1 year after IFX administration. Twenty-one tag single-nucleotide polymorphisms (SNPs) in six genes were genotyped by PCR–RFLP, PCR–HRM, or PCR–direct DNA sequencing. The frequencies of the various alleles and genotypes of each SNP were compared between responders and non-responders in three different inheritance models. A genetic test was performed using a combination of the associated SNPs as biomarkers.

The genetic analyses indicated that the frequency of a C/T genotype of rs4251580 in *IRAK4* in the minor allele dominant model was significantly decreased in responders compared with non-responders for the long-term treatment of 1 year (odds ratio [OR]: 0.289; p=0.014), indicating an approximately 3.5-fold loss of response to IFX. Conversely, a C/C genotype of rs4251580 indicated an approximately 3.5-fold increase in response to IFX (Table 1). Moreover, the possession of a T/T genotype of rs7255265 in *TICAM1* indicated an approximately 4-fold loss of response to IFX after 1 year of treatment (OR: 0.252; p=0.038). Conversely, a C/C or C/T genotype of rs7255265 showed an approximately 4-fold increase in response to IFX (Table 1). We subsequently performed a genetic test with a combination of the two independent genetic factors, *IRAK4* and *TICAM1* genotypes, which indicated that possession of both the C/C genotype of rs4251580 in *IRAK4* and the C/C or C/T genotype of rs7255265 in *TICAM1* was associated with a strong response to IFX (OR: 4.444; p=0.003). The sensitivity, specificity, positive predictive value, and negative predictive value of this genetic test were estimated at 72.2%, 63.2%, 90.9%, and 30.8%, respectively.

This is the first report demonstrating that *IRAK4* and *TICAM1* are IFX-related genes in Japanese CD patients. In the intestines of non-responder CD patients, the presence of the C/T genotype of rs4251580 in *IRAK4* and of the T/T genotype of rs7255265 in *TICAM1* may cause a slight gain-of-function in both IRAK4 and TICAM1, respectively, thereby leading to a certain level of activation of both within the TLR4 signalling pathway. Therefore, elevated production of pro-inflammatory cytokines through the activation of this signalling pathway may lead to perpetuation of the chronic intestinal inflammatory process, and may result in the secondary loss of response to IFX after 1 year of treatment. In addition, the combination of

polymorphisms in these two genes is useful as a new biomarker to predict response to IFX after 1 year of treatment. Finally, signal transduction molecules within the TLR4 signalling pathway, including IRAK4 and TICAM1, may represent novel targets for therapeutic agents aimed at overcoming the secondary loss of response to IFX treatment.

OPTIMAL CHOICE OF FIRST-LINE TREATMENT IN CROHN'S DISEASE

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Introduction: Crohn's disease (CD) is a chronic, progressive inflammatory disease that results in cumulative tissue damage and disability. Recent studies have demonstrated that thiopurines and anti-tumour necrosis factor α agents may change the natural course of disease by decreasing the need for surgery.[1,2] Therefore, there is an increasing body of evidence for us to look beyond the symptoms of CD and prevent structural damage early during the course of the disease.[3]

Aims: To review existing literature regarding the natural history of CD, possible prognostic factors associated with complicated disease outcome, definition of treatment goals and evidence for treatment choices, and to suggest an algorithm for first-line treatment options in CD.

Results: According to population-based studies, the cumulative probability of surgery after diagnosis of CD is 13% at 1 year and 38% at 10 years.[4] In addition, there is a cumulative probability of 88% that a stricturing or penetrating complication will develop during 20 years of disease duration.[5] Clinical risk factors for complicated disease course include extensive small bowel disease, upper gastrointestinal extent, early stricturing or penetrating disease, deep ulcers upon endoscopy, young age at diagnosis, smoking, and perianal lesions.[6] Conversely, mucosal healing is associated with decreased need for surgery, fewer hospitalisations, better quality of life, and steroid tapering.[7] As set out by the recent STRIDE initiative, the goals of treatment in CD are to achieve both clinical/patient-reported and endoscopic remission (or resolution of inflammation on cross-sectional imaging).[8] A close monitoring strategy is required to achieve this. Biomarker measurement (C-reactive protein, faecal calprotectin) and imaging/endoscopy is favoured to identify objective signs of inflammation 6–9 months after treatment initiation, and to determine treatment escalation. There seems to be an early 'window of opportunity' to change disease course.[9,10]

Conclusions: A rapid step-up approach based on close monitoring is recommended for the treatment of CD. Early aggressive therapy is advocated in severe or complicated disease when poor prognostic factors are present.

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WHEN SHOULD WE INTRODUCE PSYCHOLOGICAL TREATMENTS IN IRRITABLE BOWEL SYNDROME PATIENTS?

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Irritable bowel syndrome (IBS) is a common disorder, with a prevalence of 5–20% in the general population. The majority of patients can be treated in primary care settings, but the management of IBS patients accounts for up to 25% of a gastroenterologist's workload in the outpatient department. The main symptoms of IBS are abdominal pain, bloating, and altered bowel habits. The pharmacological treatment approaches currently available focus on reducing symptom severity but many patients under different treatment regimens do not show adequate symptom relief. This has led to an effectiveness gap for IBS patients and medical professionals; both are seeking additional therapeutic options. Psychological interventions are possible treatments that can reduce symptoms or increase patients' quality of life. IBS is considered to be a biopsychosocial disorder, whose onset and precipitation are a consequence of interaction among multiple factors that include motility disturbances, abnormalities of gastrointestinal sensation, gut inflammation, altered processing of afferent sensory information, psychological distress, and affective disturbances.[1]

There are three common approaches to control the symptoms associated with IBS: pharmacological agents, dietary therapies, and psychological treatments. Acknowledgment of the biopsychosocial model of illness introduces psychological therapies such as hypnotherapy, cognitive behavioural therapy (CBT), and mind–body therapy as potential remedies for gastrointestinal symptoms and improvement of quality of life in IBS patients.[1,2]

There are currently several psychological treatments that are available but not all of them have gained scientific approval. The largest amount of scientific data has been collected on gut-directed hypnotherapy (GDH) and CBT. Data on GDH show that it has an effect on various physiological indices, such as gut motility, visceral sensitivity, immune modulation, and autonomic nervous system activity. Cognitive and behavioural treatment modalities are often combined and include techniques such as systemic desensitisation, problem-solving therapy, social skills training, imagery, and homework exercises. CBT is frequently used in combination with forms of relaxation therapy and biofeedback.[2-5] Behavioural therapy aims to change the behaviours that stem from maladaptive anxiety-related cognitions (exposure, desensitisation, and behavioural experiments), while cognitive therapy is focussed on elements of cognitive restructuring of irrational or maladaptive anxiety-related cognitions.

Although studies show that other psychological therapies such as mindfulness, stress management, and relaxation training have statistically significant effects on the quality of life and symptom severity of IBS patients, these results should be interpreted with caution before we implement them into standard clinical practice.[3-5] Current meta-analyses suggest that psychological interventions might be useful in selected groups of patients but they also point out the main problem of the majority of clinical trials: small sample sizes, as well as other methodological drawbacks such as influence of placebo. Optimal placebo comparison in trials of psychological interventions remains an unresolved issue. It has been suggested that specific patient characteristics might predict the success of psychological interventions. For example, stress management might be appropriate in patients experiencing aggravation of symptoms under conditions of extra burden or in patients experiencing major life events, whereas CBT might be justified in patients with inadequate coping strategies.

To conclude, psychological therapies are effective and safe in specific groups of IBS patients who are predominantly psychologically distressed.

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SCREENING AND SEROLOGY-BASED DIAGNOSIS OF COELIAC DISEASE

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Population-based screening studies have shown the prevalence of coeliac disease to be up to 2% and rising. This makes the disease one of the most common food-related chronic conditions. Untreated coeliac disease predisposes patients to complications such as poor growth and underachievement in children, and infertility and small-bowel lymphomas in adults. An early diagnosis and treatment is mandatory in order to prevent these severe complications, and to lessen the burden of untreated disease on both patients and healthcare.[1] In order to increase diagnostic yield, screening of at-risk groups or even the whole population has been advocated. The main question regarding screening is whether only mildly symptomatic or apparently asymptomatic patients benefit from the screening. Furthermore, early antibody screening often reveals seropositive individuals with normal mucosal villi, and until now it has remained unclear if such cases should be diagnosed.

Our recent randomised trial showed that even screen-detected and apparently asymptomatic patients benefit from an early diagnosis and treatment of coeliac disease.[2] In addition, these individuals were shown to adhere to the demanding gluten-free diet and consider their serological screening as positive. The study has aroused noticeable interest within the scientific community,[3] and will likely have a major impact on the future screening policy for coeliac disease. Moreover, we have provided evidence that intestinal damage in coeliac disease develops gradually and that the coeliac autoantibodies are specific markers of the early developing disease. Furthermore, a substantial proportion of these seropositive patients may suffer from symptoms and benefit from a gluten-free diet even before villous atrophy develops.[4-7] These studies have had a substantial influence on the revised diagnostic criteria for coeliac disease published by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition, in which it was stated for the first time that mucosal biopsy could be omitted in symptomatic children with high antibody titres. The validity of these revised guidelines has been recently confirmed by us and other research groups.[8,9] In fact, our results point out that similar criteria based more on serology could also be applied to adults with a coeliac disease suspicion.

The Rising Star presentation aroused a great deal of interest in the conference audience. The main issues brought out were the possible risk of overdiagnosis with serology-based criteria and treatment of asymptomatic adults. Diagnosis of coeliac disease can indeed be difficult, particularly in patients with low-positive transglutaminase 2 antibodies. In these cases, use of further diagnostic evidence, including for instance endomysial antibodies and genetic markers of coeliac disease, are of utmost importance. However, it must be realised that the processing and interpretation of the histology samples are also prone to several errors, and the histology-based criteria may in fact have a higher risk for false

positive results compared with the objective serology. It is also true that some of the asymptomatic cases may not consider their coeliac disease diagnosis completely positive.[10] However, in my opinion these individuals should be well-informed about the potential risk of complications associated with long-term untreated coeliac disease, and at least have the option to try the dietary treatment.

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NON-CARDIAC CHEST PAIN: DIFFERENTIAL DIAGNOSIS AND CLINICAL MANAGEMENT

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CASE STUDY

Aims

- To distinguish chest pain of oesophageal origin from that of cardiac origin
- To approach non-cardiac chest pain (NCCP) patients through accurate use of diagnostic tools
- To diagnose gastro-oesophageal reflux disease (GORD)-related NCCP

Case Presentation

A 37-year-old man presented with recurring intermittent chest pain in the retrosternal and substernal area, which had been present for the last 5–6 months. The pain occurred several times each week and lasted about 15 minutes. It was not associated with exertion and increased after large and/or spicy meals. There was no evidence of heartburn, regurgitation, dysphagia, or alarming symptoms. The patient's past medical history, including psychological conditions, was unremarkable and there was no family history of coronary artery disease; his physical examination was normal. The patient first presented to the primary care physician, and his blood work and chest X-ray were normal. He was prescribed ranitidine but his symptoms failed to improve after treatment, and therefore omeprazole 40 mg once daily for 1 week was prescribed on the recommendation of a physician colleague. The pain did not improve significantly and he was referred to a gastroenterologist.

Case Discussion

Management of patients with NCCP is often challenging. Oesophageal causes of chest pain should be considered after appropriate cardiological evaluation for ischaemic heart disease. GORD is the cause of symptoms in approximately 60% of NCCP patients. It remains uncertain why some patients complain of heartburn and others of chest pain after reflux events.

Upper gastrointestinal endoscopy should be performed in patients with alarming symptoms. Otherwise, an empiric trial of proton-pump inhibitor (PPI) treatment is the most cost-effective strategy in the initial management of NCCP. Patients who fail to respond to acid suppression should undergo endoscopy with oesophageal biopsies, not only if dysphagia is also present, in order to rule out eosinophilic oesophagitis. If negative, ambulatory pH monitoring with symptom correlation is required for the differential diagnosis of GORD, hypersensitive oesophagus, and functional heartburn. The role of non-acid reflux in NCCP patients is unclear. Nevertheless, the addition of impedance to pH monitoring also detects non-acid reflux, which can be an important cause of symptoms in 'hypersensitive oesophagus'. In patients with intermittent symptoms, prolonged pH monitoring using a wireless capsule improves the sensitivity of investigation.

Following high-dose PPI treatment, patients with GORD-related NCCP display symptomatic improvement in approximately 80% of cases; the response of other patients is no better than placebo. Some patients with GORD-related NCCP require the addition of pain modulators for symptom control (e.g. low-dose antidepressants). The role of anti-reflux surgery is not well studied, but can be effective in well-selected patients.

KID: A CAPSULE ENDOSCOPY DATABASE FOR MEDICAL DECISION SUPPORT

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Computer based systems (CBS), created by integrating expert knowledge with machine learning algorithms, support medical decision-making. The use of CBS in capsule endoscopy (CE) is limited.[1] Therefore we developed KID, a publicly available and free-to-access database that aims to advance CE software research and to provide an educational resource for physicians and information technology (IT) scientists alike.[2] The KID scientific committee invites contributions of anonymised CE image and video data. The contributions should be of high quality (original resolution) and not distorted by compression. For image contributions, the recommended standard is ISO/IEC 15948 PNG (Portable Network Graphics). Other acceptable standards include popular near-lossless coding: ISO/IEC 14496-10 MPEG-4 AVC (Advanced Video Coding) and H.264. For CE-related software research, KID provides a gold standard through semantic and graphic image annotations. Annotations are supported by an open access and platform-independent annotation tool (Ratsnake).[3] Furthermore, semantic annotation is based on standard web ontology language description logics. The quality of submitted data and annotations is scrutinised by an international scientific committee; contributions not conforming with the aforementioned standards and objectives are rejected. To date, more than 1,500 annotated CE images and 47 video clips or full videos have been registered in KID. These include images of the following lesion categories: a) vascular: angiectasis and/or intraluminal bleeding; b) inflammatory: mucosal aphthae and ulcers, erythema, cobblestone, and luminal stenosis; c) lymphangiectasias: chylous cysts, nodular lymphangiectasias, punctuate lymphangiectasias; and d) polypoid lesions.[3] Datasets submitted to KID have already been used for lesion detection and size measurement by machine learning algorithms.[4,5]

In conclusion, KID provides a platform for data and knowledge exchange between clinicians with CE interest and IT researchers. It enables direct comparisons between methods for medical decision support in CE, thus leading to essential progress in the field.[2]

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SURGICAL EXCISION: SUBMUCOSAL OR TRANSMURAL? TRANSMURAL!

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Early diagnosis of colorectal neoplasia is increasing as a result of bowel screening and improved access to diagnostic services. Techniques for local treatment of early bowel lesions have entered everyday practice, but patient pathways involving gastroenterology, histopathology, radiology, oncology, and surgery are complex. The term 'early neoplasia' may describe a range of situations from a benign tumour to T1, T2, and T3a/b cancers suitable for organ-sparing treatment through the use of radiotherapy and local transanal excision.[1-3]

The role of surgical local excision is most established in the rectum. Transanal endoscopic microsurgery (TEMS), developed by Buess in the 1980s, provides a versatile platform for the treatment of early rectal neoplasia. TEMS can accomplish mucosectomy, submucosal, or full-thickness excision with suture repair of the surgical defect. The technology is well proven to be safe and its success has inspired the production of a variety of different transanal devices. In expert hands, this technology reproducibly delivers the high-quality, en bloc local excision necessary for detailed histopathological stratification of malignant tumours.[4] The only drawback is that patients must be anaesthetised.

The flexible endoscopic platform is currently less versatile than TEMS for the removal of rectal neoplasia. Tumours are removed in the submucosal plane by either endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). While this is ideal for benign tumours that sit within the mucosa, it is a potentially hazardous strategy for early malignancy as resection may be incomplete. Piecemeal EMR of malignant lesions, sometimes termed the 'whoops' polypectomy, is highly inappropriate as it prevents a standardised histopathological assessment of the tumour, leading to uncertainty and the possibility of unnecessary radical surgery.

Controversy exists regarding the role of ESD for treatment of early rectal cancer. Full-thickness surgical local excision provides high cure rates where tumours invade only a short distance into the submucosa. The Japanese have the greatest experience using ESD for treatment of these early cancers,[5] where endoscopic magnification techniques facilitate identification of appropriate stage tumours. This technology is not yet widely available in Western practice, and we have yet to show that Japanese results are reproducible in Western populations. I would suggest that direct extrapolation of the Japanese experience into Western practice is currently premature. Patients with 'significant rectal neoplasia' should receive expert multidisciplinary evaluation with the aim of optimising pre-treatment cancer diagnosis and subsequent interventions through clinical studies that record patient outcomes, such as the STAR-TReC study that will open soon in the UK, Denmark, and the Netherlands.

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OBESITY AND CANCER: IS IT AN EPIDEMIC?

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Is obesity an epidemic? And how does obesity link with the cancer epidemic? Firstly, we need to consider how we define an epidemic. Although traditionally applied to infectious diseases, an epidemic has two key components: (i) it affects a large proportion of the population, and (ii) it has spread rapidly. Does obesity fit with these two components?

Using the definition of obesity as a body mass index (BMI) of 30 kg/m^2 or above, we know that large regions of the world now have at least one-fifth of adults being classified as obese.[1] Data on long-term trends of obesity also show that prevalence has increased from 10% to 30% in the US between 1990 and 2010.[2] Therefore – and forgive the puns – the terms 'affecting a large proportion' and 'rapid spread' can undoubtedly be applied to obesity. However, the obesity epidemic also affects multiple countries and continents, and so the term epidemic does not do justice to our global obesity problem. We are, in fact, in the midst of an obesity pandemic!

But how does the obesity pandemic fit with our knowledge of cancer trends? Comparing global maps of obesity prevalence[1] and cancer incidence[3] shows remarkable ecological correlation. Generally, the two disease trends fit; however, there are nuances to consider, such as differences in cancer site, sex, geographic region, ethnicity, histological subtypes, and molecular features.[4] Excess body weight is most strongly associated with two 'groups' of cancers: digestive tract cancers (with the notable exceptions of oesophageal squamous cell carcinoma and gastric cancer) and hormonal cancers (with the notable exception of premenopausal breast cancer).[5]

Despite the known associations between obesity and cancer risk, there has been no clear association between BMI and cancer progression and survival in studies conducted to date.[6-8] However, the most appropriate timing of body weight measurement in epidemiological studies of obesity and cancer survival is proving to be complex. We may also need to consider molecular epidemiology in further detail. To highlight just one example of this important new interdisciplinary field, Morikawa and colleagues[9] have demonstrated that *TP53* positivity on colorectal cancer-specific survival differs significantly by BMI. The adverse effect of *TP53* positivity on patient mortality was limited to non-obese patients.[9] It is becoming clearer that lifestyle factors, including obesity, may impact both the molecular phenotype of tumours that develop and the resulting prognosis for the patient.

However, an important epidemiological concept has been somewhat overlooked – the temporality of the association between obesity and cancer. Edgren et al.[10] have highlighted that the large increase in oesophageal adenocarcinoma incidence seen in recent years does, in fact, pre-date the obesity pandemic. They hypothesise that an exposure change in the 1950s is more likely to explain these trends. Our decline in physical activity levels and increase in sedentary behaviour since the mid-20th century[11] may correspond more closely with global cancer trends than obesity per se.

Lastly, to draw an analogy from tobacco smoking and cancer research, we know that quitting smoking will reduce your risk of developing cancer in the future. Major efforts are now being invested in behavioural change research to reduce obesity and increase physical activity levels. However, we still do not know whether being obese and then losing weight, or becoming more physically active, will have the same reduction in risk or improved outlook for cancer survival as quitting smoking does.[12]

Other important topics that were raised by the audience in response to this talk included the importance of childhood obesity trends, separating out excess caloric intake from obesity and physical inactivity, and understanding what determines the

time lag between exposure to obesity (and other lifestyle factors) and cancer development. While the epidemiology community struggle to overcome confounding and measurement issues in studying these associations, working together with basic and translational researchers who have the ability to conduct tightly controlled experiments will play a key role in enhancing our understanding of these challenges in obesity and cancer.

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ACUTE-ON-CHRONIC LIVER FAILURE IN PATIENTS WITH CIRRHOSIS: IS IT A DISTINCT ENTITY? NO

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Acute-on-chronic liver failure (ACLF) first appeared as a term in the medical literature in 2002. However, actual data on the condition only emerged with the results of the CANONIC (CLIF Acute-on-Chronic Liver Failure in Cirrhosis) study in 2013. There have been various definitions proposed, including those from the Asian Pacific Association for the Study of the Liver, the Chronic Liver Failure Consortium, the North American Consortium for the Study of End-Stage Liver Disease (NACSELD), and those recently proposed by the World Congress Of Gastroenterology. None of these definitions have been prospectively validated. For ACLF to be considered as a distinct entity, several criteria need to be met: a) a prospectively validated definition that differentiates the condition from acute liver failure and acute decompensation; b) clearly defined pathophysiology; c) distinct laboratory and clinical characteristics; and d) an externally validated scoring system for prognosis. None of these criteria have been met to date.

The CANONIC study was designed in order to identify a group of patients with cirrhosis who have a 1-month mortality of more than 15%; these patients were classified as having ACLF. The researchers concluded that the greater the number of failing organs, the higher the mortality. They also concluded that younger patients with no previous decompensation were at higher risk of dying. Since they did not capture alcoholic hepatitis in their study, however, the latter could well represent alcoholic hepatitis. This particular finding was not replicated in the NACSELD data or the Chinese data reported by Sei et al.

Therefore, based on available data, ACLF does not represent a distinct entity. Its role at the moment is to identify those patients with cirrhosis and acute decompensation who are at greater risk of dying. Prospectively collected data are needed, including an exact definition of this condition.

HEPATITIS C

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Within the last 4 years, treatment of chronic hepatitis C virus (HCV) has undergone a revolution. The previous treatment with peginterferon/ribavirin has been replaced by interferon (and hopefully soon ribavirin)-free regimens, which are far more effective and better tolerated.

Today, we have three substance classes of direct-acting antivirals, which are used in various combinations (see Table 1). All of them are very effective (with sustained virological response rates of >90%) and have a good safety profile. Each regimen targets genotype (GT)1 patients, but not all of them are active against other genotypes or in patients with decompensated cirrhosis (Child–Pugh score B or C). The safety of some combinations has not been studied yet (see Table 2). Furthermore, the optimal duration of treatment (8–24 weeks) and the need for the addition of ribavirin requires further studies. Ribavirin only improves the efficacy by a few percent in GT1a patients if protease inhibitors are used, but is responsible for most side effects of the therapy.

Ideally, all patients infected with HCV should receive one of these treatment regimens, but for economic reasons they are restricted to patients with more advanced liver disease or are not available at all.

Table 1: Licensed (or soon to be licensed) direct-acting antivirals.

	Licensed			In development	
Protease inhibitors	Simeprevir	Paritaprevir	Asunaprevir (only in Japan)	Grazoprevir	
NS5A inhibitors	Daclatasvir	Ombitasvir	Ledipasvir*	Velpatasvir	Elbasvir
Polymerase inhibitors	Sofosbuvir	Dasabuvir			

*Single fixed-dose combination with sofosbuvir, ombitasvir+paritaprevir.

Table 2: Use of direct-acting antivirals according to patient characteristics.

	SOF/LDV	SOF/DCV	SOF/SMV	3D	2D	SOF/RBV
GT1a	✓	✓	✓	✓	No	No
GT1b	✓	✓	✓	✓	✓?	No
GT2	No	No	No	No	No	✓
GT3	?	✓	No	No	No	✓
GT4	✓		✓	✓	✓	
Noncirrhotic	✓	✓	✓	✓	✓	
Cirrhosis CPS A	✓	✓	✓	✓	✓	No
Cirrhosis CPS B/C	✓	✓	?	No	No	No
Post-OLT F0–2, CPS A	✓	✓	✓	✓		No
Post-OLT F3–4, CPS A–C	✓	✓	?	No		No
Renal impairment	?	?	?	✓		No

GT: genotype; CPS: Child–Pugh score; SOF: sofosbuvir; LDV: ledipasvir; DCV: daclatasvir; SMV: simeprevir; 2D: ombitasvir+paritaprevir; 3D: 2D+dasabuvir; RBV: ribavirin; OLT: orthotopic liver transplantation.

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CYSTIC PANCREATIC LESIONS BEYOND THE GUIDELINES: CAN WE MAKE AN EVIDENCE-BASED DECISION WHETHER TO RESECT OR TO OBSERVE?

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ABSTRACT

Pancreatic cystic neoplasms (PCNs) are no longer considered as rare entities because their prevalence in the general population ranges from 3–20%. They are usually asymptomatic, incidentally discovered, and diagnosed in the seventh decade of life. The main clinical concern with regard to PCNs is related to their risk of malignant progression, which is relevant for those PCNs that produce mucin. Since 2006, several sets of international guidelines have proposed algorithms for the management of PCNs, and these have been subsequently validated by several studies. Retrospective review of the literature shows that current treatment of PCNs remains unsatisfactory because the guidelines are based on a low level of evidence. However, the guidelines are able to correctly identify lesions that can be safely followed and, as occurs in vaccination campaigns, they are able to exercise a preventive effect in the general population.

Keywords: Pancreatic cyst, cystic neoplasm of the pancreas, intraductal papillary mucinous neoplasms, mucinous, serous, Sendai, Fukuoka, guidelines, pancreatic cancer.

INTRODUCTION: FROM THE ORIGINS TO THE GUIDELINES ERA

The increasing prevalence of pancreatic cystic neoplasms (PCNs) during previous decades has led to the use of the term 'technopathies' to describe this heterogeneous group of tumours. In fact, the increasing use of high-quality, cross-sectional imaging in clinical practice has played the major role in the discovery and subsequent characterisation of these entities. It has been estimated that 3–14% of the general population has at least one PCN.[1-4] After the first report describing a PCN was published in the early 1980s,[5] an increasing number of case reports and clinical studies focussing on pancreatic cysts have been published. In daily clinical practice, clinicians face a high and increasing number of PCNs and must deal with the risk of either over or undertreatment of patients due to our currently incomplete knowledge of their biological behaviour. In the present article we summarise the most prominent publications defining the clinical and radiological aspects of PCNs, which were obtained following a comprehensive review of the literature; these publications range from articles describing original research to consensus guidelines based on various, generally low levels of evidence.

Intraductal papillary mucinous neoplasms (IPMNs), mucinous cystic neoplasms (MCNs), and serous cystic neoplasms (SCNs) represent the most frequently observed entities in the family of PCNs. There are several other rare types of PCN with a very low prevalence,[6] but a full description of these is beyond the aims of the present review and therefore not included. Whenever a patient with suspected PCN is referred to a specialist, the typical clinical picture is that of an asymptomatic and nonspecific lesion in the pancreatic parenchyma. Identification of the lesion's cystic nature is often easily achieved via the initial diagnostic workup. However, the definition of the specific subtype of PCN (IPMN, MCN, or SCN) and the consequent risk of malignancy represents a

challenging diagnostic dilemma. For example, the connection between the cyst and the pancreatic ductal system, which differentiates the diagnosis of an IPMN from that of an MCN, can be difficult to assess even with high-quality, cross-sectional imaging. Moreover, the presence of a multicystic pattern is more frequently associated with SCNs (Figure 1), but a small oligocystic mass in the body/tail of the pancreas offers a difficult differential diagnosis between an SCN and an MCN. In many cases, only surgical resection provides a definitive diagnosis, and the rate of error can be as high as 30% at high-volume centres.[7]

The first landmark in the development of a policy for the diagnosis and treatment of PCNs was the publication of the international consensus guidelines in 2006.[8] These 'Sendai guidelines' greatly contributed to increasing awareness regarding PCNs and facilitated further studies (Table 1).[8-11]

INTERNATIONAL SENDAI CONSENSUS GUIDELINES (2006)

Since reducing the risk of a misdiagnosis represents a critical issue for pancreatic specialists, the Sendai guidelines contain practical indications that are useful for the prediction of malignancy in a pancreatic cyst. Historically, IPMNs involving the main duct (MD-IPMNs; Figure 2) have been considered as a major indication for resection because they have a high likelihood of harbouring malignancy.[12] During imaging, this type of PCN frequently appears as a dilatation of the main pancreatic duct (MPD) rather than an obvious cystic lesion, with a diameter between 5 and 9 mm considered as presumptive for the diagnosis. Mixed-type IPMNs (MT-IPMNs) have been categorised together with MD-IPMNs because the involvement of the MPD is the principal determinant of the tumour's biology. In contrast, indications as to whether to resect or not are less evident when a cystic neoplasm develops at a site distal from the MPD. The Sendai guidelines specify the dimensions of the cyst as being the main parameter, with an empirical 3 cm threshold. Even if no other 'worrisome features' are present, recommendation to schedule the patient for resection is given by this parameter alone. Other indications to resect a cystic neoplasm are the presence of mural nodules, symptoms such as jaundice or pancreatitis, MPD dilatation >6 mm, and positive cytology. The 2006 Sendai guidelines have been validated by a number of case series,[13-18] with diagnostic sensitivity shown to be extremely high, but approximately 75% of the resections were performed on tumours found to be benign/borderline. The morbidity and mortality rates associated with pancreatic resections, which are as high as 40% and 3% respectively,[19] demand a superior means of predicting malignancy so that unnecessary procedures can be avoided.

INTERNATIONAL FUKUOKA CONSENSUS GUIDELINES (2012)

The volume of literature and new evidence that became available following the publication of the Sendai guidelines advocated for an update. The new 'Fukuoka guidelines' stratified pancreatic cysts into different categories depending on their characteristics and related clinical symptoms.[9] Jaundice, enhancing solid component in the cyst, and an MPD size >10 mm have been defined as 'high-risk stigmata', and their presence indicates resection because of a relevant association with an invasive tumour in 6–27% of cases.[14] A cyst size >3 cm, thick or enhancing cyst walls, non-enhancing nodules, MPD size between 5 and 9 mm, abrupt change in MPD calibre with concomitant atrophy, and suspect lymphadenopathy or pancreatitis are worrisome features, and should undergo a second-level follow-up with endoscopic ultrasonography (EUS). At this point, if any mural nodules, involvement of MPD, or suspicious/positive cytology are detected, then resection is warranted. In the absence of both high-risk stigmata and worrisome features, the dimension of the cyst represents the crucial parameter to establish the correct timing of the follow-up.

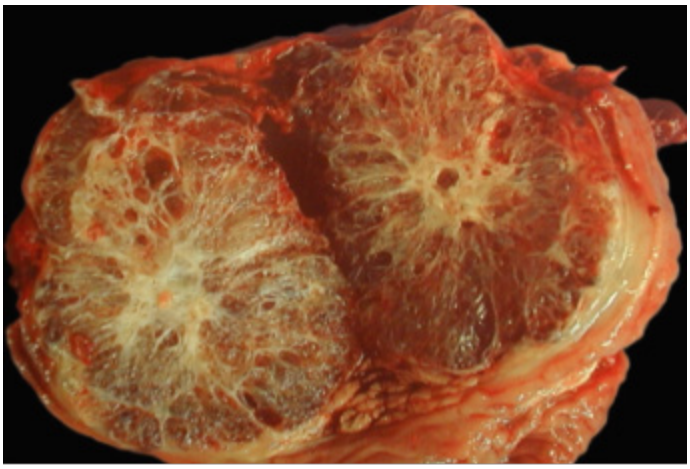

Figure 1: Gross pathology of a serous cystic neoplasm.

Table 1: Current clinical guidelines on the management of pancreatic cystic neoplasms.

Sendai consensus guidelines[8] (applied to all mucin-producing pancreatic cystic neoplasms)	
MD-IPMN	MPD >10 mm
Sendai-positive BD-IPMN	Size >3 cm Size <3 cm with symptoms, mural nodules, MPD dilatation >6 mm, and/or positive cytology
Fukuoka consensus guidelines[9] (applied to all mucin-producing pancreatic cystic neoplasms)	
High-risk stigmata	Proximal lesion with obstructive jaundice Enhancing nodules Dilated MPD >10 mm
Worrisome features	Size >3 cm Pancreatitis Non-enhancing mural nodules Thickened, enhancing walls Dilated MPD (5–10 mm) Change in MPD calibre with distal atrophy Lymphadenopathy
European consensus guidelines[10] (applied to all mucin-producing pancreatic cystic neoplasms)	
Risk factors	Symptoms Size >4 cm Mural nodules Dilated MPD >6 mm Elevated CA 19-9 (relative risk)
American Gastroenterological Association guidelines[11] (applied to asymptomatic mucinous cysts)	
Low risk	Size <3 cm No solid component
High risk	Size >3 cm Dilated MPD Solid component Concerning feature on EUS

BD-IPMN: branch-duct intraductal papillary mucinous neoplasm; CA 19-9: carbohydrate antigen 19-9; EUS: endoscopic ultrasonography; MD-IPMN: main-duct intraductal papillary mucinous neoplasm; MPD: main pancreatic duct.

The most relevant novelty of these guidelines is a more conservative approach towards mucinous-producing cystic tumours, which aimed to reduce the false-positive rate for malignancy compared with the previous version.

EUROPEAN EXPERTS CONSENSUS STATEMENT ON PCNS (2013)

Another 'experts' consensus meeting' was held in 2013, this time in Europe, and brand new guidelines for the management of cystic neoplasms of the pancreas were generated.[10] The trend towards a more conservative approach dependent on the size of the cyst was confirmed, with a cut-off size of 4 cm used for deciding whether to resect a tumour or not. There needs to be a note of caution with this cut-off value, however, because malignancy can be found in smaller lesions too, with a frequency of up to 25% in lesions <4 cm.[9] However, this risk needs to be considered alongside the risk of mortality associated with a major pancreatic resection. Other indications to resect a PCN are the related symptoms, mural nodules, MPD ≥6 mm, elevated serum carbohydrate antigen 19-9, and an increase in cyst size >2 mm/year. With regards to diagnostic methodology, both computed tomography (CT) and magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) are considered the gold standard, whilst EUS with fine-needle aspiration (FNA) should be reserved for selected cases because of its low accuracy and inter-observer variability.[20-22]

Several sets of national guidelines have been published since 2013, such as the Italian guidelines in 2014, but the level of evidence remains low and unable to provide substantially different indications to support decision-making.[23]

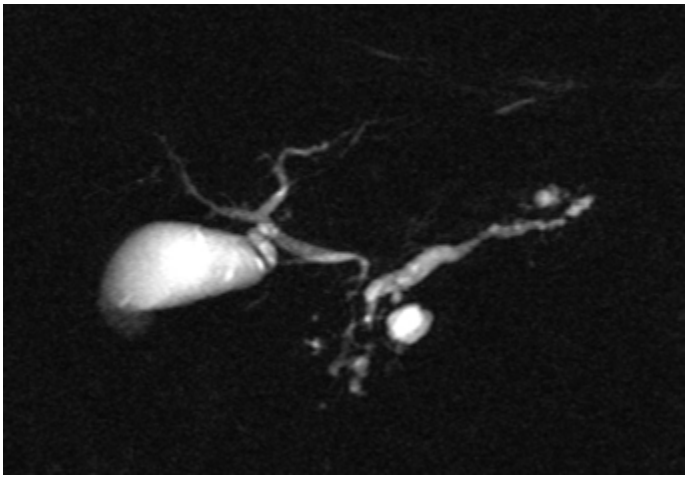

Figure 2: Magnetic resonance cholangiopancreatography of a mixed-type intraductal papillary mucinous neoplasm.

AMERICAN GASTROENTEROLOGICAL ASSOCIATION INSTITUTE GUIDELINES ON THE DIAGNOSIS AND MANAGEMENT OF ASYMPTOMATIC PCNS (2015)

The most recent policy in the field is represented by the American Gastroenterological Association (AGA) guidelines published in 2015.[11] The AGA guidelines refer only to asymptomatic cysts of the pancreas with side-branch involvement; MD-IPMN, symptomatic cysts, and cystic differentiation of other malignant tumours are therefore excluded. According to the AGA guidelines, cysts <3 cm and without solid components or dilated MPD can be followed up through MRI. Cysts with ≥2 high-risk features, such as size >3 cm, dilated MPD, or presence of solid components should undergo EUS-FNA to better assess the risk of malignancy. Patients without concerning results from EUS-FNA could be followed up with MRI, although the negative predictive value of FNA is low. Significant changes during the surveillance programme represent an indication for subsequent EUS risk assessment. After 5 years of follow-up, or whenever a patient is no longer a surgical candidate, radiological surveillance may be discontinued. Finally, surgical resection is advocated when either a solid component and MPD dilatation is found, or when there are concerning results from EUS or positive cytology.

THE MANAGEMENT OF PANCREATIC CYSTS BEYOND THE GUIDELINES

The first and foremost result of the publication of international guidelines by world-renowned experts has been to increase awareness that PCNs are entities that are not as uncommon as previously thought. At the same time, internal policies on the management of PCNs at different centres with expertise in the field have been rearranged and modified according to the guidelines. As a result, a bulk of literature with a focus of validating the guidelines has been published, with the 2-fold aim of assessing their accuracy and possibly improving them.

The first data that can be extracted from the post-guidelines literature are the standardisation of diagnosis and research of PCNs. Clinicians and gastrointestinal specialists all over the world have acknowledged that tomographic imaging through CT and MRI with MRCP represents the first fundamental step in correctly assessing a cystic lesion in the pancreas.[8] In this regard, EUS-FNA is now considered a second-level examination and is not systematically indicated as a first approach to guide the management strategy.[9] In experienced hands, EUS can be a valid diagnostic tool for detecting solid components in PCNs, the relationship with the ductal system, septa, and cystic fluid features.[24] However, it remains an operator-sensitive technique and the addition of cytological examination can even reduce its sensitivity because there is low inter-observer agreement in defining cytology grading for PCNs.[21] Other diagnostic tools, such as positron emission tomography, have not reached a sufficient level of accuracy for defining the features of PCNs and predicting their biological behaviour, and therefore do not have a role in either the initial work-up or the follow-up. However, the main concept when assessing the true nature of a PCN is that diagnostic accuracy is low, even in the setting of a correct algorithm used at high-volume centres.[7] As the possibility to correctly define a PCN is, by definition, only possible at pathological examination, most of the studies validating the guidelines are retrospective surgical series.

In contrast to what can be extrapolated from the policies of the guidelines, debate on the correct management of SCNs still exists. We are now aware that the growth rate can be predicted by the morphological features and follows a bimodal curve.[25] These factors should be taken into account

in decision making and integrate the guideline concept that serous cystic adenomas (SCAs) should not be resected. The fact that malignant SCAs are practically non-existent has been reinforced by a recent large multi-institutional series of 1,363 resected cases, in which only three were invasive (0.2%).[26] With regard to MCNs, surgical series validating the guideline policy to always resect this premalignant neoplasm have shown low rates of either high-grade dysplasia or invasive cancers ranging from 5.5–13.4% and 3.9–12%, respectively.[8,27,28] Moreover, combining the results of six major studies that met International Academy of Pathology criteria for diagnosis of MCNs showed that only 0.26% of MCNs <3 cm in diameter were malignant.[28-33] Indeed, the authors of these recent studies suggest following up MCNs of small dimensions and in the absence of solid components.[34-36] Among all PCNs, IPMNs represent by far the most debated entity in terms of assessing the reliability of the guidelines. Further large series have shown that the Sendai guidelines lack specificity, so that the more recent Fukuoka guidelines have a more conservative approach in order to prevent unnecessary pancreatic surgeries, as high-risk stigmata, jaundice, and enhancing nodules have had their predictive value for malignancy confirmed.[13,15,16] The correct cut-off for MPD size has been debated more, because reducing the cut-off value to 5 mm seems to improve its accuracy as a predictor of malignancy.[15,16] However, the most controversial parameter of those taken into account as predictors of malignancy in IPMNs is the diameter of the cyst. Several studies have tested the 3 cm cut-off in order to assess the risk of malignancy, and most of them have concluded that it seems reasonable to continue observing a small PCN in the absence of other triggers for surgery.[13,15-18] Other studies have claimed the opposite, however, and have reported relevant rates of malignancy, even in small branch-duct IPMN (BD-IPMN) <3 cm.[37-40] All of the other worrisome features, such as thick or enhancing cyst walls, non-enhancing nodules, abrupt change in MPD with distal atrophy, pancreatitis, and the presence of lymphadenopathy, have been variably associated with malignancy. However, whenever a statistically significant correlation has been identified, the diagnostic value was fairly poor, with low specificity and sensitivity.[13-16,18] The application of both the Sendai and Fukuoka guidelines has been very recently evaluated in 1,382 resected patients by Goh and colleagues.[14] The revised guidelines have a low positive predictive value ranging from 27–62% and with an overall value of 36%. The stratification of cases into two subgroups at different risk results in an improved positive predictive value of 66% in the group of patients displaying high-risk stigmata. Moreover, the negative predictive value ranges from 82–100%. In their conclusions, the authors point out that a relevant cohort of IPMNs classified as 'low risk of malignancy' showed either high-grade dysplasia or invasive carcinoma.[14] With regard to the surveillance of BD-IPMN, it seems reasonable to follow up lesions not presenting with high-risk stigmata. Large observational studies have shown that a minority of the patients will undergo surgery for cysts that increase in size or due to the development of symptoms (around 20%), and practically none of these will be found with unresectable cancer.[17]

DISCUSSION

In multiple fields of surgical oncology, clinical guidelines are needed in order to guide clinicians when taking crucial decisions in the management of patients. In this regard, PCNs do not represent an exception, especially because of their recent discovery and presumed relatively low prevalence in the general population. Now we are aware that PCNs are not rare entities thanks to the widespread use of tomographic imaging. Moreover, increasing evidence has been published during the last decades and expert opinions are being tested by the data coming from surgical series. Unfortunately, because of the peculiar biology of the disease, randomised controlled trials capable of achieving the appropriate level of evidence are far from being established. At the same time, we are aware that the use of experts' opinions as guidelines represents the bottom of the 'evidence pyramid', and that they should represent the starting point of a scientific process instead of a fixed policy.

Analysis of literature published after the different international guidelines and aiming to validate their accuracy has raised several important issues. SCNs do not represent an indication for surgery and undergo resection mainly due to a diagnostic error or because they cause mass-related symptoms.[25] Mucin-producing cystic neoplasms still represent a potential indication for surgery because the literature has failed to exclude their potential to progress to invasive carcinoma. However, the guidelines and subsequent literature reveal the need for parameters able to determine whether

the risk of harbouring invasive carcinoma exceeds that arising from a difficult surgical procedure. Surgeons are aware that pancreatic resections carry with them a relevant risk of both morbidity and mortality, even nowadays and at high-volume centres.[41] In this setting, surgeons are aware that they are not operating on a cyst, but on an individual who has a 3% likelihood of dying because of the procedure and a risk of serious complications that exceeds 30%. There are no truly 'minimally invasive' procedures to remove pancreatic neoplasms, which is in contrast to other types of premalignant lesions that can be safely excised whilst at a premalignant stage, such as colon polyps. Enucleations and laparoscopic techniques are also burdened with relevant rates of morbidity,[42,43] and clinicians should always keep this in mind during decision-making. At the same time, accurate analysis of the guidelines and subsequent literature has revealed that leaving a potentially fatal tumour technically amenable to resection in the pancreas should be considered as a fatal mistake. In fact, guidelines more prone to a significant rate of false-positive cysts seem more acceptable than those leading to the opposite type of diagnostic error. In this setting, the policies of the Fukuoka guidelines with respect of IPMNs have been shown to be fairly safe. Debate still remains because recent publications on small 'negative-for-resection-criteria' IPMNs have reported high rates of malignancy.[37,44] These data appear difficult to read, and one may speculate that the different ways in which different pathologists classify the same grade of dysplasia may be having an effect in this setting. The need for a 'common language' in the pathological assessment of PCNs was recently highlighted at a multidisciplinary expert meeting held in Verona. The aim of the meeting was not to generate new guidelines, but to find a way to increase the level of evidence in the field. Indeed, the first study promoted by those in attendance has led to a standardisation of the definitions used by pathologists with regard to PCNs.[45]

The new AGA guidelines were published almost immediately after the scientific community appeared to be moving towards a common method of promoting more multicentric prospective studies aimed at improving the level of evidence in the post-guidelines era. Far from being evaluated in validation studies, the AGA guidelines importantly disclose that they are based on low-quality evidence. It therefore looks unlikely that they could fill the gaps between international policies and local clinical practice. In fact, the trend towards a more conservative approach, even for mucinous PCNs, in past years demands answers from large cohort studies with long-term follow-up. Moreover, expectations are growing regarding the use of molecular analyses of cystic fluid and other next-generation biomarkers to improve our ability to predict the risk of progression to malignancy in a specific lesion.[22]

CONCLUSIONS

The question of whether to resect or to observe PCNs is still far from being answered in an evidence-based setting. Critical analysis of the available guidelines indicates that their application in clinical practice seems to resemble the effect of vaccinations; they are able to 'protect' the vast majority of the population affected by a PCN. Mistakes cannot be totally avoided, however, because we cannot guarantee each patient that our policies are 100% safe with regard to not missing a malignant tumour or resecting a benign one. Only large prospective studies will help us to increase our knowledge and drive clinical practice forward by allowing us to tailor treatment to individual patients.

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MANAGEMENT OF DIVERTICULITIS AND PREVENTION OF RECURRENCE

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ABSTRACT

Acute diverticulitis is an acute inflammation of colonic diverticulae that is associated with an episode of severe, prolonged, lower abdominal pain (usually on the left side), changes in bowel movements, low-grade fever, and leukocytosis. Acute diverticulitis is a significant burden in industrialised societies, accounting for 313,000 hospitalisations in the USA alone, and a trend of rising incidence has been observed. Despite the high prevalence, the management of diverticulitis and post-diverticulitis is largely based on consensus more than evidence derived from randomised clinical trials. In this review we will focus on the diagnosis and management strategies for diverticulitis and post-diverticulitis.

Keywords: Diverticular disease, diverticulitis, management, risk factors, therapy.

INTRODUCTION

The prevalence of colonic diverticulae in the general population is estimated to range from 20–60%.[1,2] The mere presence of colonic diverticulae is defined as diverticulosis. The term 'diverticular disease' (DD) implies that the diverticulae have given rise to illness. An acute inflammation of colonic diverticulae is defined as acute diverticulitis.[2] The natural history of DD is poorly understood. Early population-based, retrospective studies showed that patients with diverticulosis display a 10–25% lifetime risk of developing acute diverticulitis.[2,3] A recent population-based cohort study reappraised the risk of developing diverticulitis: in a survival analysis of 2,222 patients with diverticulosis incidentally discovered during colonoscopy, only 95 patients (4.3%; 6 cases per 1,000 patient-years) developed diverticulitis over an 11-year follow-up period.[4] However, DD accounts for 313,000 hospitalisations in the USA and is the fifth most common reason for ambulatory care visits.[1]

CLINICAL FEATURES OF ACUTE DIVERTICULITIS

Acute diverticulitis is associated with an episode of severe, prolonged, lower abdominal pain (usually on the left side), changes in bowel movements, low-grade fever, and leukocytosis.[5,6] The true incidence of diverticulitis is unknown because population studies have only considered patients admitted to hospital, whereas many patients without a systemic inflammatory response or known diagnosis of DD are treated for episodes of abdominal pain in primary care, which leads to an underestimation of the true incidence of the disease.[5] However, several studies have reported an increase in the incidence of acute diverticulitis, with an overall age-adjusted increase in hospital admissions from 61.8 per 100,000 hospitalisations to 75.5 per 100,000 hospitalisations in the USA from 1998–2005.[7]

RISK FACTORS

Lifestyle factors and ageing are considered two major risk factors for the development of diverticulitis and its complications. The following lifestyle factors have been evaluated in terms of

the risk of symptom development: physical activity, diet (including fibre content and nut, corn, and popcorn consumption), smoking, and obesity. Strate et al.[8] evaluated the role of physical activity in DD during an 18-year follow-up and found that men in the highest quintile of vigorous physical activity had a 25% risk reduction for developing diverticulitis compared with men who exercised the least.

The EPIC-Oxford study has examined the relationship between dietary fibre intake and risk of hospitalisation for DD. A cohort of 47,033 healthy individuals was followed-up for 5 years and showed that patients with a high fibre intake (>25 g/day) had a 41% lower risk of hospitalisation compared to those with the lowest fibre intake (<14 g/day).[9] Regarding the consumption of certain foods, Strate et al.[10] reported that the consumption of nuts, corn, and popcorn does not increase the risk of diverticulitis and its complications.

Tobacco consumption is associated with several inflammatory conditions. In the EPIC-Oxford cohort, individuals who smoked <15 cigarettes per day had a relative risk of hospitalisation for DD of 1.34, whereas those who smoked ≥15 cigarettes per day had a relative risk of 1.86, compared with non-smokers.[9] Similarly, in a retrospective Italian study, current smokers had an increased risk of diverticulitis compared with non-smokers (odds ratio: 2.79; 95% confidence interval: 1.30–5.96).[11]

Obesity has also been established as a major risk factor for diverticulitis. Men with a body mass index (BMI) >30 kg/m^2 displayed a 78% higher risk of diverticulitis compared with men with a BMI <21 kg/m^2 in an 18-year follow-up of 47,000 men.[12]

Several studies have also shown an association between drug use and diverticulitis. These findings have important clinical implications given the prevalence of DD in the elderly. In a large prospective study, an increased risk of diverticulitis and diverticular bleeding was observed among users of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs).[13] Furthermore, there is evidence that the use of opiate analgesics and oral corticosteroids is associated with an increased risk of diverticulitis complications, such as perforation.[14]

CLINICAL PRESENTATION

The clinical manifestations of acute diverticulitis vary with the extent of the inflammatory process. In classical cases, patients report abdominal pain that localises to the left lower quadrant, which may be associated with nausea or vomiting and a change in bowel habits (diarrhoea or constipation). Suprapubic or right-sided pain may also be reported by some patients with a large and redundant sigmoid colon. Diffuse abdominal pain associated with peritoneal signs suggests complicated disease, such as free perforation, whereas absolute constipation may be due to an underlying obstruction. Dysuria is a common symptom reported by patients and is secondary to irritation of the bladder by the inflammatory process.

On physical examination, findings vary according to the severity of the inflammation: fever and tachycardia may be present. The patient may present with pain and localised rigidity in the left lower quadrant, whereas patients may present with a rigid board-like abdomen in cases with inflammatory extension of the peritoneum. Bowel sounds may be depressed (paralytic ileus) or increased (obstruction). Table 1 shows the clinical features observed in a study reviewing 741 cases of acute diverticulitis.[15]

Several other diseases can have a similar presentation and mimic acute diverticulitis. For this reason, alternative diagnoses for lower abdominal pain must be considered. In particular, it may be necessary to rule out appendicitis, inflammatory bowel disease, colon cancer, cystitis, pelvic inflammatory disease, and infectious colitis.[5]

Table 1: Clinical features of acute diverticulitis.[15]

Clinical feature	Frequency (N=741)
Abdominal pain	97.6%
Pain in lower abdomen	82.7%
Pain not limited to lower abdomen	17.3%
Nausea	38.0%
Vomiting	16.2%
Diarrhoea	23.2%
Constipation	14.0%
Rectal bleeding	6.8%
Abdominal tenderness	89.2%
Fever	30.1%
Leukocytes >11,000/mm^3	58.5%

DIAGNOSIS

In cases of abdominal pain, laboratory tests should be performed in order to evaluate the inflammatory state and to exclude other potential causes. Blood tests such as a full blood count, creatinine, C-reactive protein, amylase, and lipase are required, as is urine analysis to exclude urinary tract infection. The double-contrast enema is not currently in use because the extramural component of inflammation is more important than the intramural inflammation for the staging of acute diverticulitis. Computed tomography (CT) is considered as the initial radiological examination because of its high sensitivity (93–97%) and a specificity for diagnosis approaching 100%,[16] but also because CT allows the physician to evaluate the extent and complications of diverticulitis.[17] Alternatively, evidence supports the role of ultrasound (US) examination in the management of diverticulitis. The primary advantage of US is that it does not require exposure to radiation and is widespread. However, the accuracy of US is often dependent on the skill of the examiner. In addition, CT has the potential to provide more information on alternative causes of abdominal pain. In a comparative study, the sensitivity of CT was slightly superior (91% versus 85%) whilst US displayed slightly superior specificity (85% versus 77%).[18]

In recent years, magnetic resonance imaging (MRI) has also been introduced for the diagnosis of DD and acute diverticulitis. In a study conducted in Germany, the sensitivity and specificity of MRI colonoscopy were calculated as 86% and 92%, respectively.[19] As with double-contrast enema, colonoscopy does not provide information about the extramural component of inflammation. In addition, colonoscopy should be avoided in acute diverticulitis because of the risk of perforation.

STAGING

The most commonly used criteria for scoring the severity of diverticulitis is Hinchey's system. Hinchey's classification categorises peritonitis as one of four stages.[20] Patients with Stage 1 have small, confined, pericolic abscesses. Stage 2 disease is characterised by larger abscesses, often confined to the pelvis. Stage 3 disease is present when a peridiverticular abscess has ruptured, leading to a purulent peritonitis. Lastly, Stage 4 is characterised by faecal contamination of the peritoneal cavity. Although it does not consider the systemic inflammatory response or patient features (i.e. age, immunosuppression, and comorbidities), Hinchey's classification is useful in clinical practice: the risk of death is <5% for patients with Stage 1 or 2 diverticulitis, 13% for those with Stage 3, and 43% for those with Stage 4.[21]

TREATMENT

Management and treatment approaches depend on the severity and complexity (i.e. presence of an abscess, fistula, and/or perforation) of the condition. For patients with mild acute diverticulitis, outpatient therapy with oral, broad-spectrum antibiotics is reasonable. A combination of metronidazole and ciprofloxacin is often used, but other regimens are also effective (Table 2). A review of 92 publications identified the following criteria for hospitalisation in cases of mild acute diverticulitis: significant inflammation, intolerance to oral fluids, no response to oral antibiotic therapy, age >80–85 years, and presence of immunosuppression or comorbidities (e.g. diabetes, chronic renal failure, malignant haematological diseases, HIV infection, chemotherapy, steroid therapy, or transplantation).[22]

Table 2: Drug regimens commonly used to treat diverticulitis.[21]

Oral regimens	Intravenous regimens
Metronidazole (500 mg every 6-8 hr) + quinolone (e.g. ciprofloxacin 500-750 mg every 12 hr)	Metronidazole (500 mg every 6-8 hr) + quinolone (e.g. ciprofloxacin 400 mg every 12 hr)
Metronidazole (500 mg every 6-8 hr) + trimethoprim–sulfamethoxazole (160 mg trimethoprim and 800 mg sulfamethoxazole every 12 hr)	Metronidazole (500 mg every 6-8 hr) + third-generation cephalosporin (e.g. ceftriaxone 1-2 g every 24 hr)
Amoxicillin–clavulanate (875 mg every 12 hr)	Beta-lactam with a beta-lactamase inhibitor (e.g. ampicillin–sulbactam 3 g every 6 hr)

All clinical guidelines recommend hospitalisation, bowel rest, and broad-spectrum antibiotics in severe and/or complicated acute diverticulitis not in need of emergency surgery. These patients should be treated with intravenous antibiotics active against aerobic and anaerobic bacteria. Recommended drug combination regimens are based more on clinical consensus than on evidence from randomised clinical trials (RCTs; Table 2).[6]

For patients in whom diverticulitis is complicated by peridiverticular abscess, the size of the abscess is an important determinant of treatment success: small pericolic abscesses (<4 cm in diameter) can be treated conservatively with bowel rest and antibiotics, while larger abscesses (>4 cm) are more likely amenable to CT-guided percutaneous drainage.[6]

Despite the lack of RCTs comparing antibiotic treatment with no antibiotic treatment, conservative management with bowel rest and antibiotics is considered the standard of care for non-complicated acute diverticulitis. However, in recent years several studies have compared antibiotic treatment with no antibiotic treatment in mild acute diverticulitis. In a retrospective audit of 311 patients hospitalised for acute diverticulitis at a single hospital in Sweden, Hjern et al.[23] observed that managing acute diverticulitis without antibiotics leads to no increase in adverse events compared with antibiotic management, with a similar rate of recurrence also observed. In a recent multicentre RCT in Sweden, 623 patients with CT-verified, acute, uncomplicated, left-sided diverticulitis were randomised to treatment with or without antibiotics. The results of the study reveal that antibiotic use does not reduce the risk of complications (abscess or perforation) or the 1-year recurrence rate, and nor does it accelerate recovery.[24] Although suggestive, at the present time there is not yet enough evidence for this strategy to be adopted into clinical practice. Further data will accrue from another large, pragmatic, multicentre RCT (the DIABOLO trial) comparing treatment with and without antibiotics. Patients will be randomised to a conservative strategy (antibiotics for 10 days, hospital admission, and supportive measures) or to a liberal strategy (no antibiotics, supportive measures, and admission on clinical grounds only if necessary).

PREVENTION OF RECURRENCE

The natural history of DD is not fully understood. Few studies have explored the course of acute diverticulitis and the recurrence rate of diverticulitis. A retrospective study analysing 337 patients with uncomplicated diverticulitis and 165 with complicated diverticulitis, with a median follow-up of 101 months, reported an overall recurrence rate of 18.8% for one episode of recurrence and 4.7% for two or more episodes, with no statistically significant difference between the two patient groups in terms of the rate of recurrence.[25] In a study performed using the California Office of Statewide Health Planning and Development database, 179,649 patients admitted for diverticulitis and managed medically were analysed and, of these, 27,450 (16.3%) suffered a second episode of diverticulitis. The risk factors for recurrence included: age <50 years, smoking, obesity, female sex, complicated presentation, previous diagnosis of diverticulosis, and chronic use of NSAIDs.[26]

The primary goal in the management of patients with a history of diverticulitis is the prevention of a subsequent episode. However, there are many issues in this field because of the lack of studies regarding secondary prevention of acute diverticulitis. In addition, the studies available are often of low quality and include a small number of patients. To date, the management of post-diverticulitis is based more on consensus than on RCT data.[27] A high daily fibre intake, especially insoluble fibre, appears to be a good strategy, although no clear evidence is available.[6]

The use of antibiotics may promote the selection of non-pathogenic strains of intestinal bacterial flora, thereby reducing the risk of diverticulitis. A recent, multicentre, randomised, open trial studied the efficacy of rifaximin, in addition to a high-fibre dietary regimen, in the secondary prevention of acute diverticulitis. Rifaximin plus high-fibre proved to be more effective than high-fibre alone in the secondary prevention of acute diverticulitis, with a recurrence rate at 12 months of 10.4% in patients given rifaximin plus high-fibre versus 19.3% in patients receiving high-fibre alone (p=0.033).[28] Further studies are needed to confirm these results.

Several studies have investigated the role of mesalazine in the secondary prevention of diverticulitis. However, two Phase III, double-

blind, placebo-controlled, multicentre RCTs have evaluated the efficacy of multimatrix mesalazine versus placebo for the prevention of recurrent diverticulitis in 590 (PREVENT1) and 592 (PREVENT2) adult patients with ≥1 episodes of acute diverticulitis in the previous 24 months.[29] No significant difference in the rate of diverticulitis recurrence was observed among treatment groups at Week 104. In addition, mesalazine did not reduce the time to recurrence, and the proportion of patients requiring surgery was comparable between treatment groups. Given this evidence, there is no clear proof that mesalazine reduces the rate of diverticulitis recurrence.[6]

ELECTIVE SURGERY

In the past, statements from scientific associations agreed on the need for a prophylactic sigmoidectomy after two previous episodes of acute diverticulitis.[30,31] Recent studies have shown a more benign natural history of DD, with a low rate of recurrence. Therefore, a less aggressive surgical policy has been suggested.[32] In fact, elective surgery should be recommended in patients with symptomatic, complicated DD (e.g. fistula, stenosis). In other cases, the indication to perform elective colectomy resection should not be based on the number of previous episodes of diverticulitis but should be evaluated by balancing the severity of symptoms, risk of severe recurrences, and morbidity due to surgery.[6]

CONCLUSION

Acute diverticulitis is a significant burden in industrialised countries. Despite the high prevalence of the disease, there are many issues regarding therapeutic management. It is known that lifestyle factors (diet, obesity, smoking, drug use) play a critical role in the development of the first episode and recurrence. The optimal clinical management of an episode of acute diverticulitis is currently under debate; bowel rest and broad-spectrum antibiotics are the most common strategies. Preliminary data on management without antibiotics support this strategy for mild diverticulitis. Complicated diverticulitis needs a case-by-case evaluation and further studies are needed to understand the best medical management strategy.

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AN UPDATE ON THE TREATMENT OF *HELICOBACTER PYLORI* INFECTION

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ABSTRACT

Helicobacter pylori treatment is becoming a challenge in light of increasing antimicrobial resistance and falling eradication rates. This is a cause for concern based on the complications of *H. pylori* infection, which include gastric and peptic ulcers, gastric cancer, and mucosa-associated lymphoid tissue lymphoma. This review discusses recent data assessing the current treatment options for *H. pylori* infection and the importance of considering the prevalence of antibiotic resistance at a regional level when choosing an appropriate therapy. Alternatives to the standard first-line treatment, such as bismuth and non-bismuth quadruple therapies, are outlined and rescue therapies involving levofloxacin and rifabutin are also reviewed.

Keywords: *Helicobacter pylori,* triple therapy, bismuth quadruple therapy, sequential therapy, concomitant therapy, hybrid therapy, antibiotic resistance.

INTRODUCTION

Helicobacter pylori is a gram-negative bacterium that specifically colonises the stomachs of approximately 50% of the global population.[1] Infection is usually acquired in early childhood and, despite triggering a vigorous immune response, *H. pylori* persists for life if left untreated. The prevalence of *H. pylori* infection varies throughout the world and is associated with older age and with lower socioeconomic conditions.[1] Although most infected individuals do not develop any significant symptoms, *H. pylori* is causally linked to a number of gastrointestinal disorders; peptic ulcers develop in 1–10% of those infected, while gastric cancer and gastric mucosa-associated lymphoid tissue lymphoma present in 0.1–3% and <0.01% of infected individuals, respectively.[2] The World Health Organization's International Agency for Research on Cancer has classified *H. pylori* as a definite (Group 1) carcinogen.[3] *H. pylori* infection has also been linked to unexplained iron-deficiency anaemia and idiopathic thrombocytopenic purpura, with recent guidelines on the management of these conditions recommending *H. pylori* eradication where present.[4,5]

Consensus guidelines on the management of *H. pylori* infection recommend a standard first-line triple therapy that consists of an acid-suppressing proton pump inhibitor (PPI; 20–40 mg) together with the antibiotics clarithromycin (500 mg) and amoxicillin (1,000 mg) taken twice daily for 7–14 days (Table 1).[6-8] Metronidazole (500 mg) is used instead of amoxicillin in penicillin-allergic individuals. Unfortunately, the success rate of first-line triple therapy has fallen in many countries, with eradication rates of just 55–57% reported from countries in Western Europe.[9,10] A number of factors contribute to treatment failure, including high bacterial load, low gastric pH, and impaired mucosal immunity,[11] although the main reasons for *H. pylori* treatment failure are thought to be poor compliance and antimicrobial resistance.[6,11-13] Several strategies have been shown to improve the efficacy of standard triple therapy. A recently published meta-analysis has shown that increasing the duration of triple therapy involving a PPI, amoxicillin, and clarithromycin from 7 to 10 days results in a significantly higher eradication rate (76.2% versus 80.5%, respectively).[14] Fourteen days was found to provide the most effective eradication rate (85.8%).[14] Increasing the dose of PPIs also has

a positive effect on treatment outcome, as PPIs increase gastric pH, reduce gastric juice volume, and delay gastric emptying, thus preventing acid-related antibiotic degradation and increasing gastric levels of antibiotics.[15,16] If initial therapy fails, however, a levofloxacin-based rescue therapy is recommended.[6,13] If subsequent treatment is required, rifabutin-based regimens may be prescribed,[6,17] but treatment should be guided by antimicrobial susceptibility testing.[6]

H. PYLORI ANTIBIOTIC RESISTANCE

The antibiotics used for eradication of *H. pylori* target pathways that disrupt bacterial homeostasis or replication. The use of more than one antibiotic in each treatment regimen enables targeting of *H. pylori* viability through multiple pathways, thereby increasing the likelihood of successful eradication. Amoxicillin is included in most treatment regimens as resistance to this antibiotic is low. Amoxicillin is a β-lactam antibiotic that acts by interfering with bacterial peptidoglycan synthesis, in particular by blocking transporter proteins called penicillin-binding proteins. Mutations in the *pbp-1a* gene have been reported to confer amoxicillin resistance.[18,19] Clarithromycin is a macrolide antibiotic that binds to the 23S ribosomal subunit of *H. pylori*, thus preventing bacterial protein synthesis. Single point mutations (most commonly A2146C, A2146G, and A2147G) within the *H. pylori rrl* gene that encodes the 23S ribosomal subunit confer clarithromycin resistance.[19] Levofloxacin belongs to the fluoroquinolone family of antibiotics that target the DNA gyrase enzyme involved in DNA strain relief during bacterial replication. The most significant mutations conferring quinolone resistance are located at positions 87 (N87K) and 91 (D91N, D91G, D91Y) of the *H. pylori gyrA* gene, which encodes the A subunit of the DNA gyrase enzyme.[20] Metronidazole is a nitroimidazole antibiotic that functions as a pro-drug that is non-enzymatically reduced to a molecule that destabilises bacterial DNA, resulting in bacterial cell death.[19] In terms of metronidazole resistance, a definitive panel of resistance-associated point mutations has not yet been characterised, although mutations in the *H. pylori rdxA* and *frxA* genes have been implicated.[19] Although the mutations mediating tetracycline and rifabutin resistance have been described, resistance to these antibiotics is low in most regions.[21-23] The mechanism of action of tetracycline is interference with protein synthesis at the ribosomal level. Tetracycline resistance is associated with mutations in the 16S rRNA gene.[18,19]

Table 1: *Helicobacter pylori* treatment regimens.

Therapy	Description
Standard triple therapy	PPI*, 500 mg clarithromycin, and 1,000 mg amoxicillin (twice daily for 7–14 days)
Bismuth quadruple therapy**	PPI* (twice daily), 120–600 mg bismuth salt, 250–500 mg metronidazole, and 250–500 mg tetracycline (up to four times daily for 7–14 days)
Sequential therapy	PPI* and 1,000 mg amoxicillin (twice daily for 5–7 days) followed by PPI*, 500 mg clarithromycin, and 500 mg metronidazole (twice daily for 5–7 days)
Concomitant therapy	PPI*, 1,000 mg amoxicillin, 500 mg clarithromycin, and 500 mg metronidazole/tinidazole (twice daily for 7–14 days)
Hybrid therapy	PPI*, 1,000 mg amoxicillin (twice daily for 14 days) with 500 mg clarithromycin and 500 mg tinidazole (twice daily for the final 7 days)
Levofloxacin-based triple therapy	PPI*, 250 mg levofloxacin, and 1,000 mg amoxicillin (twice daily for 7–14 days)
Levofloxacin-based sequential therapy	PPI* and 1,000 mg amoxicillin (twice daily for 5 days) followed by PPI*, 250 mg levofloxacin, and 500 mg metronidazole (twice daily for 5 days)
Rifabutin-based triple therapy	PPI*, 1,000 mg amoxicillin, and 150 mg rifabutin (twice daily for 7–14 days)

*PPI dose: 20 mg omeprazole, 20 mg rabeprazole, 30 mg lansoprazole, 40 mg esomeprazole, or 40 mg pantoprazole; **Variations in the dose of bismuth quadruple therapy have been reported.
PPI: proton pump inhibitor.

Table 2: Recent data on the prevalence of *Helicobacter pylori* antibiotic resistance.

Region	Resistance rate Clar	Resistance rate Met	Resistance rate Lev	Reference
China, Beijing	37.2%**	63.9%**	50.3%**	26
China, south-east coastal region	21.5%**	95.4%**	20.6%**	27
Europe, northern countries	7.7%*	28.6%*	7.7%*	21
Europe, southern countries	21.5%*	29.7%*	13.1%*	21
Europe, western and central countries	18.7%*	43.8%*	18.6%*	21
Japan	38.8%* 55.6%**	ND ND	34%* 38.6%**	28
Latin America	12%*	53%*	15%*	29
Senegal	1%*	85%*	15%*	30
Thailand	3.7%*	36%*	7.2%*	23
USA	16.4%**	20.3%**	31.3%**	24

*Primary resistance rate; **Overall resistance rate.
Clar: clarithromycin; Met: metronidazole; Lev: levofloxacin; ND: not determined.

Table 3: *Helicobacter pylori* treatment strategies based on local clarithromycin resistance patterns.

Treatment	Option	Low clarithromycin resistance (<15–20%)	High clarithromycin resistance (>15–20%)
First-line	A	Clarithromycin-based triple therapy*	Bismuth quadruple therapy
	B	Bismuth quadruple therapy	Non-bismuth quadruple therapy (sequential**, concomitant, or hybrid)
Second-line	A	Levofloxacin-based triple therapy†	
	B	Bismuth quadruple therapy‡	
Subsequent	A	Guided by antimicrobial susceptibility testing	
	B	Rifabutin-based triple therapy	

*14 days triple therapy with high-dose proton pump inhibitor (e.g. 40 mg esomeprazole twice daily) demonstrates the best eradication rates; **Not suitable in areas with high rates of dual clarithromycin and metronidazole resistance; †Unless local data indicate high rates of quinolone resistance; ‡Unless already used in first-line therapy.

Rifabutin is a spiro-piperidyl-rifamycin antibiotic that targets the β subunit of the DNA-directed RNA polymerase encoded by the *rpoB* gene; mutations in this gene confer rifabutin resistance.[19]

H. pylori antibiotic resistance is thought to develop due to the outgrowth of a small existing population of resistant organisms. Primary antibiotic resistance refers to *H. pylori* antibiotic resistance in individuals with no previous *H. pylori* eradication therapy. Secondary antibiotic resistance results when a susceptible strain acquires resistance during the course of a treatment. In both cases, resistance is thought to occur due to inappropriate antibiotic use. There exists a clear link between *H. pylori* antibiotic resistance and previous antibiotic use. Analysis of cumulative and yearly outpatient antibiotic consumption in Europe revealed a significant association between the use of long-acting macrolides and resistance of *H. pylori* to clarithromycin, and between previous quinolone use and levofloxacin resistance.[21]

Studies on the prevalence of antibiotic resistance in the UK and USA have also shown previous antibiotic use increases the risk of harbouring resistant strains of *H. pylori*.[22,24]

The most recent assessment of primary antibiotic resistance in Europe reported overall resistance rates for clarithromycin, levofloxacin, and metronidazole of 17.5%, 14.1%, and 34.9%, respectively, with a prevalence ≤1% for tetracycline, rifampicin, and amoxicillin.[21] Almost 8% of strains isolated had combined resistance to metronidazole and clarithromycin. The rate of clarithromycin resistance had almost doubled since the previous European survey,[25] which is a cause for concern as clarithromycin resistance decreases the efficacy of standard first-line triple therapy by up to 70%.[6] Metronidazole resistance was high at 34.9%,[21] but the level had not changed significantly since the previous Europe-wide study.[25] The impact of metronidazole resistance on *H. pylori* eradication is less than that of clarithromycin resistance, and can be overcome by increasing the dose and duration of treatment or by prescription of bismuth-containing quadruple therapy.[9]

Interestingly, variations in the prevalence of antibiotic resistance across European countries were observed (recent data summarised in Table 2).[26-30] The resistance rate for clarithromycin was <10% in northern European countries, while most countries in the rest of Europe (except Spain and Germany) had a resistance rate of >15%.[21] Such variations in antibiotic resistance have also been reported at a local level within countries. For example, a recent study in the UK indicated that the resistance rates to clarithromycin, metronidazole, and quinolones in Wales were 18%, 43%, and 13%, respectively, but in England were 3%, 22%, and 1%, respectively.[22] Differences in resistance rates have also been reported outside Europe (Table 2). For example, although the overall resistance rates for clarithromycin, metronidazole, and levofloxacin in Thailand were 3.7%, 36%, and 7.2%, respectively, metronidazole resistance was more prevalent in southern Thailand than north-eastern Thailand (66.7% versus 33.3%).[23] Such diversity in the prevalence of antibiotic resistance has important consequences when it comes to choosing the appropriate therapy for successfully eradicating *H. pylori* in a given population. According to the Maastricht IV guidelines, standard triple therapy should now only be prescribed in regions where the prevalence of clarithromycin resistance is known to be <15–20% (Table 3).[6]

While no new drug has been developed as a direct replacement, recent trials have assessed the efficacies of therapies involving different combinations of known antibiotics, the results of which are discussed below.

BISMUTH QUADRUPLE THERAPY

Bismuth quadruple therapy (Table 1) has been recommended as a first-line therapy in regions of high clarithromycin resistance, and in areas with low clarithromycin resistance as an alternative to standard triple therapy or as a rescue regimen.[6] A recent meta-analysis reported eradication rates of 77.6% and 68.9% for bismuth quadruple therapy and standard triple therapy, respectively.[31] Compliance and adverse events were similar across the two treatment groups and bismuth quadruple therapy did not appear to be affected by metronidazole resistance. Variations in the bismuth therapy treatment regimens were described in terms of antibiotic dose and treatment duration. A sub-analysis of the data showed that, although bismuth therapy for 10 days was more effective than 7 days of triple therapy, the two therapies given for the same length of time yielded similar eradication rates.[31] In keeping with the idea that the duration of bismuth quadruple therapy affects eradication success, a 95% eradication rate for a 14-day bismuth therapy regimen has been described.[32]

In terms of rescue therapy, a meta-analysis by Marin et al.[13] indicated that when bismuth-containing quadruple therapy was prescribed following failure of standard clarithromycin-based triple therapy, the eradication rates were 76%, 77%, and 82% for 7, 10, and 14 days, respectively. In addition, high *H. pylori* eradication rates with bismuth therapy have been described in patients who did not respond to previous therapies, including those with metronidazole resistance.[33-35] Taken together, these findings support a role for bismuth quadruple therapies as both first-line and rescue regimens. However, due to the unavailability of tetracycline and bismuth salts in several countries, bismuth quadruple therapy may not always represent an accessible treatment option.[13,36]

NON-BISMUTH QUADRUPLE THERAPY

Sequential Therapy

Non-bismuth quadruple therapy has been proposed as an alternative to bismuth quadruple

therapy for first-line treatment in regions with high clarithromycin resistance.[6] The efficacy of sequential therapy (Table 1) compared with triple therapy, however, depends on the treatment durations under comparison and the study population. A systematic review and meta-analysis performed by Gatta et al.,[37] which compared 46 randomised controlled trials, indicated that sequential therapy was superior to 7-day triple therapy, marginally superior to 10-day triple therapy, but not superior to 14-day triple therapy. Geographic variations in the prevalence of antibiotic resistance appear to be a key factor affecting the lack of difference between sequential therapy and 14-day triple therapy, as a meta-analysis by Losurdo et al.[38] reported that sequential therapy was superior to 14-day triple therapy in areas with high clarithromycin resistance, but sequential and triple therapy were similar in areas of high metronidazole resistance. Of note, the Gatta study[37] described an overall eradication rate of just 37% for sequential therapy in patients infected with *H. pylori* strains resistant to both clarithromycin and metronidazole resistance, indicating that dual antibiotic resistance significantly impacts the efficacy of sequential therapy.

Concomitant Therapy

Standard triple therapy can be converted to concomitant therapy (Table 1) by the addition of 500 mg of metronidazole or tinidazole twice daily. A meta-analysis of the randomised controlled trials comparing concomitant with standard triple therapy revealed eradication rates of 90% and 78% for concomitant and triple therapy, respectively, by intention-to-treat analysis.[39] The analysis indicated that clarithromycin resistance may impact the efficacy of concomitant therapy, but to a lesser extent than standard triple therapy.[39] A recent multicentre trial in Spain comparing 14-day triple therapy with 14-day concomitant therapy revealed that the extended concomitant therapy achieved significantly higher cure rates (>90%) compared with 14-day triple therapy, with milder adverse events and no effect on compliance.[15] Evidence to date suggests similar eradication rates when concomitant therapy is compared with sequential therapy, with no significant differences in terms of compliance or adverse events.[36,37,40,41] Therefore, while the eradication rates for concomitant and sequential therapy appear similar, both appear superior to standard triple therapy as a first-line treatment option.

Hybrid Therapy

The recently described hybrid therapy represents a combined version of sequential and concomitant therapy, comprising a PPI (20–40 mg) with amoxicillin (1,000 mg) for 14 days plus clarithromycin (500 mg) and a nitroimidazole derivative (500 mg) for the final 7 days (Table 1). Hsu et al.[42] initially reported eradication rates of >90% for hybrid therapy. However, it is unclear whether hybrid therapy has any significant advantage over sequential or concomitant therapy, as recent meta-analyses of trials to date demonstrated similar eradication rates across all three therapies.[43,44] Further studies in additional countries are required in order to determine whether hybrid therapy exhibits improved efficacy over sequential or concomitant therapy as a first-line therapy.

SECOND-LINE AND SUBSEQUENT *H. PYLORI* ERADICATION THERAPIES

Following failure of standard triple therapy, a levofloxacin-based rescue therapy (Table 1) is recommended unless local data indicate high rates of quinolone resistance.[6,13] Meta-analyses have shown that 10 days of levofloxacin triple therapy is superior to bismuth quadruple therapy, but not 7 days of levofloxacin therapy.[45,46] The inclusion of levofloxacin in sequential therapy has also been shown to be effective for patients who have failed either sequential or triple therapy.[47] Indeed, an analysis of three studies comparing sequential therapy with sequential therapy containing levofloxacin (instead of clarithromycin) demonstrated increased eradication success using the modified sequential therapy.[32] Combining levofloxacin and bismuth in patients who have previously failed *H. pylori* treatment has also been demonstrated to be a successful strategy for *H. pylori* eradication.[48] As levofloxacin resistance is emerging in many countries,[21] rifabutin-based triple therapy has been suggested as an alternative rescue therapy. Primary *H. pylori* rifabutin resistance is low[49] and rifabutin is effective in patients with dual metronidazole and clarithromycin resistance.[17] As a fourth-line therapy, Gisbert et al.[50] have provided a rationale for the use of rifabutin-based therapy as a valid rescue strategy following multiple eradication failures.

TAILORING THERAPY BASED ON ANTIBIOTIC RESISTANCE DATA

Given that antibiotic resistance impacts treatment outcome and rates of resistance vary between different regions, surveillance of antibiotic resistance represents a key strategy in choosing the appropriate first-line *H. pylori* treatment regimen in a given population. Culture of *H. pylori* from gastric biopsy specimens and antimicrobial susceptibility testing by means of minimum inhibitory concentration determination has been considered the gold standard for assessing *H. pylori* antibiotic resistance to date. However, *H. pylori* is a fastidious bacterium and culture is time-consuming and often challenging, with low sensitivity values.[51] Molecular testing for *H. pylori* antibiotic resistance offers an attractive alternative to culture and allows for analysis of *H. pylori* DNA directly from biopsy samples, providing a key opportunity for same-day diagnosis. In addition, molecular tests have been used to analyse stool samples,[52,53] potentially enabling *H. pylori* antimicrobial susceptibility testing through non-invasive procedures. In addition to surveillance, evidence from numerous studies provides a rationale for tailoring treatment based on antimicrobial susceptibility testing to improve the efficacy of both first-line[54-56] and rescue therapies.[57,58] Cost-effectiveness of tailored therapy is a genuine consideration, but it is thought to be economically viable, especially in areas of high clarithromycin resistance.[54,55]

SUMMARY

H. pylori antibiotic resistance exhibits regional variations and is constantly evolving. As such, local resistance data is imperative in guiding efficacious treatment choices (summarised in Table 3). In regions where high clarithromycin resistance has been detected, evidence supports the use of both bismuth and non-bismuth quadruple therapies as first-line alternatives to standard triple therapy. Levofloxacin-based rescue therapies are useful in areas of low quinolone resistance, while rifabutin offers a promising alternative if levofloxacin resistance is detected or following multiple treatment failures. Treatment duration is a key factor in *H. pylori* eradication success, with studies demonstrating that increasing the treatment duration improves the efficacy of all of the therapies discussed above. However, longer treatment durations may affect compliance, and therefore adherence should be strongly emphasised for the first and any subsequent *H. pylori* eradication therapies.

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PERFECT OR FAILED ERCP: WHAT MAKES THE DIFFERENCE?

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ABSTRACT

Endoscopic retrograde cholangiopancreatography (ERCP) has become an effective and safe therapeutic method, providing clinical success in more than 80% of cases. As ERCP has evolved from a diagnostic to a therapeutic procedure, technical demands have risen. Furthermore, it is an invasive procedure that can be potentially harmful when administered improperly. Quality of ERCP and procedural outcome are dependent on various factors that are related to the patient, procedure, and endoscopist. These factors are reviewed in detail and their contribution to ERCP quality is presented and discussed. Preventive therapies through procedural techniques and medical management to avoid complications are available. Proper and organised training and ERCP outcome reporting are essential for further quality improvement.

Keywords: Endoscopic retrograde cholangiopancreatography (ERCP), failure, cannulation, precut, efficiency, complications.

INTRODUCTION

Advances in endoscopic retrograde cholangiopancreatography (ERCP), sphincterotomy, and related techniques have progressively created a comprehensive grouping of therapeutic procedures. These have substantially changed the approach to diseases of the bile ducts and pancreas, and their impact can now be compared with that of laparoscopic surgery. ERCP and its associated methods have quickly spread throughout clinical practice in developed countries, are readily available, and can respond to demand without delay. Today, the majority of the interventions required in diseases of the bile ducts and pancreas can be performed by these methods and usually in a smart way – or at least we endoscopists assume so. How much do we know of the clinical experience with ERCP? How representative and reproducible are the data on these methods? How effective are they? How often do they fail when applied in the general population, and what makes the difference between success and failure? We are concerned that our data are still selective and fragmentary, and cover the issue like a mostly incomplete mosaic. Results are systematically reported only by tertiary care centres, with the data focussed on technical achievements because the overwhelming majority of procedures are done on an outpatient basis with limited patient follow-up. Consequently, our awareness of complications is also limited. We can only speculate that the less active centres and less experienced practitioners are understandably reluctant to share their possibly inferior results and numerous side effects. The achievements and complications of endoscopic methods are not consistently defined, described, classified, or researched. Admittedly, the willingness to report and share data might also be influenced by the security of personal and patient data and legal obstacles.

OUTCOME MEASUREMENT

As with other therapeutic strategies, ERCP-related methods are only meaningful if they provide consistent, sustained relief and cure. The clinical outcomes are difficult to measure because ERCP is used to treat different diseases with different

therapeutic needs, often on an outpatient basis. Therefore, surrogate characteristics are usually utilised in order to evaluate the efficacy of these procedures, including procedural technical achievements and short-term occurrence of complications. According to recently published American Society for Gastrointestinal Endoscopy practice guidelines, technical achievements and other quality indicators are classified as pre, intra, and postprocedural process measures. The most important of these include appropriateness of indication, obtaining informed consent, use of antibiotics, whether the procedure has been performed by a trained and credentialed endoscopist, volume of ERCPs performed per endoscopist, deep cannulation of the ducts of interest in a naïve papilla without altered anatomy, extraction of common bile duct stones <1 cm in diameter, stent placement in obstructions below the bifurcation, completeness of the ERCP report, all adverse events with particular emphasis on pancreatitis, perforation, and bleeding, and contact with the patient with the aim to detect delayed complications. Perhaps surprisingly, prevention of post-ERCP pancreatitis (PEP) is not addressed.

In general, our aim is a perfect ERCP, which can be characterised using the quality indicators as making a significant contribution to the diagnosis, immediate access to treatment within a single session, acceptable tolerability for the patient, successful treatment without complications, and a complete report including the indication, analgosedation, prevention of complications, details of the technique and accessories used, outcome, and recommendation. Outcomes assessed should include stone extraction rate, fluoroscopy time, and rate of successful stent placement. Conversely, a failed procedure means that deep cannulation was not achieved, diagnosis was not established, treatment was not completed, or side effects occurred.[1]

The outcome of each procedure is affected by several factors, including the indication, American Society of Anesthesiology (ASA) Grade Estimated Comorbidities score, sedation, anatomy of the upper gastrointestinal tract, equipment, technique, experience and skill of the provider, prevention of complications, and the reporting method.

ERCP EFFICIENCY

The intraprocedural quality of ERCP has been evaluated in several multicentre assessments. A retrospective analysis by DeBenedet et al.[2] selected 52 of 8,005 retrieved publications for evaluation and showed that bile duct cannulation was achieved in 89.3% (77–98.6%), the precut utilisation rate was 10.5%, common bile duct stones were successfully removed in 88.3% of procedures, and biliary stenting below the junction was achieved in 97.5%. A subgroup analysis showed no statistically significant differences between academic and community settings and in trainee participation. Peng et al.[3] prospectively analysed anonymous, self-reported procedures in a web-based registry of cases involving 3 continents, 85 endoscopists (60 USA, 16 UK, and 9 in other countries), and 13,018 ERCPs including 6,732 out patient procedures. A total of 3,746 procedures (28.8%) were described as difficulty level 3; 30.5% were labelled as ASA score III–V, either propofol with anaesthesiologist monitoring or general anaesthesia was used in 55.3%, and trainees participated in 31.6% of the procedures. Initial deep cannulation without precut was achieved in 89.9% (63.9–100%), and precut was performed in 6.7%, giving a final cannulation rate of 95.6%. The mean duration of the procedures was 25 minutes. The experience of endoscopists with ERCP was a median 12 years (range: 0–36), the median lifetime volume was 1,200 procedures (range: 175–15,000), and the median annual volume was 150 procedures (range: 10–940). Success was more likely in outpatients (odds ratio [OR]: 1.21) and with trainee involvement. The major factors predicting failure included high ERCP difficulty level (OR: 0.59), ASA score III–V (OR: 0.77), obstructive jaundice without stones (OR: 0.51), postsurgically altered bile duct anatomy (OR: 0.51), teaching cases (OR: 0.53), and certain indications (e.g. strictures or acute pancreatitis).

As expected, reports from less developed countries, where expertise and availability of instruments and medical devices are limited, are relatively rare. A study from Peru reported the results of 202 ERCPs performed within 2 years, with a failure rate of 17.3% and overall complication rate of 5.9%.[4] Peñaloza-Ramírez et al.[5] reported a success rate of 79.6% and a complication rate of 7.6% in 381 ERCPs performed over a period of 2 years in Bogota, Colombia. Gurung et al.[6] retrospectively analysed the results of 423 ERCP procedures conducted from August 2011 to August 2013 at a centre in Nepal. The cannulation rate was 94.1%, with PEP occurring in 4%.

CANNULATION TECHNIQUE

The cannulation rate can be influenced by the cannulation technique used, which can be by contrast injection (CI), with the assistance of a guidewire (GW), the 'double-wire' technique, or after precut. The contrast-assisted method and wire-guided cannulation have been compared in many studies and meta-analyses. Two meta-analyses published in 2009 showed better cannulation rates and less PEP with GW assistance (cannulation with GW: 85.3%, cannulation with CI: 74.9%; PEP OR: 0.23;[7] cannulation with GW: 89%, cannulation with CI: 78%; rate of PEP with GW: 3.2%, rate of PEP with CI: 8.7%).[8] Five comparative studies and one meta-analysis have subsequently been published. Two randomised controlled studies reported equal cannulation success and PEP rates (cannulation with GW: 83%, cannulation with CI: 87%; rate of PEP with GW: 6.1%, rate of PEP with CI: 6.3%;[9] rate of PEP with cannulation with or without GW: 5.9% and 4%, respectively; rate of PEP with sphincterotome with or without GW: 2.1% and 2%, respectively).[10] In a meta-analysis published in 2013, incidence of PEP was lower in GW groups (OR: 0.51), the cannulation rate was higher (OR: 1.07), and need for precut was lower (OR: 0.75).[11]

With the so-called double-wire technique, involving primary inadvertent but repeat cannulation of the pancreatic duct, the first wire remains in the pancreatic duct and the second wire is inserted in the presumed direction of the biliary orifice. As the PEP rate is likely to be higher with this technique, temporary pancreatic stenting is recommended.[12]

FAILED CANNULATION

In procedures involving difficult cannulation, the options to consider include: a repeat procedure 1 or 2 days later; referral to another endoscopist; continuation with the technique used; switching to another cannulation technique or precut.

Desirable deep cannulation by an experienced endoscopist using standard techniques is successful in approximately 85–90% of cases. Cannulation becomes difficult in about 5–10% of cases, especially in patients with altered anatomy, ampullary tumours, inflammatory changes of the intestine due to pancreatitis, juxtapapillary diverticula, and particularly with a modulated papillary shape. In the latter case, access to the bile duct can be achieved by a blind cut performed using either the Erlangen sphincterotome with or without the GW inserted into the pancreatic duct, or by the needle knife, in which case the precut can start either in the orifice or on the plica longitudinalis above the orifice (fistulotomy). PEP can be prevented by the temporary insertion of a pancreatic stent. There is debate regarding the optimal technique and the timing and safety of the precut. Many studies found an increased risk of PEP with this technique, but it remains unclear whether the increased rate of PEP is related to the precut itself or to prolonged cannulation. Recently, two meta-analyses were published in the same year. A review by Navaneethan et al.[13] aimed to study the cannulation rate and complications of early precut compared with persistent attempts at standard cannulation. The cannulation rate with the first technique was 90% versus 86.3% with the second. The PEP rates were not significantly different (3.9% versus 6.1%), and the overall occurrence of complications was nearly the same with the two techniques. In the seven studies reviewed, timing varied between 5 and 12 minutes; a needle knife was used in six studies, and a sphincterotome was used in one. Choudhary et al.[14] analysed the same seven randomised trials plus an additional seven non-randomised comparative trials. The analyses differ in the terminology of precut techniques (needle knife: six, sphincterotome: one in the study by Navaneethan et al.;[13] papillotomy: four, fistulotomy: two, and both techniques: one in the study by Choudhary et al.).[14] Similarly to the first study, Choudhary et al.[14] found a nonsignificant trend in favour of precut.

CASE VOLUME

Other important issues including the endoscopist's experience, case volume, and case mix have been addressed in several studies. Varadarajulu et al.[15] examined health-related outcomes after ERCP in relation to hospital procedure volume using the National Inpatient Sample database. Data from 2,629 hospitals and 199,625 ERCPs in the USA were evaluated. The median number of ERCPs performed in participating hospitals was 49 per year (range: 1–1,004), with 25% of hospitals performing ≥100 ERCPs per year and 5% performing ≥200 per year. Multivariate regression analysis found significant negative relationships between procedure volume and procedure failure rates, but did not find a significant effect on inpatient mortality.

Williams et al.[16] aimed to identify the principal risk factors for ERCP complications in a prospective analysis of results from 66 study centres and 5,264 ERCPs at the institutional level. Neither the number of ERCPs performed annually nor the hospital type (i.e. district versus university hospital) was significantly associated with overall complication rates. Nevertheless, in a subgroup of patients with pancreatitis, the risk of PEP was significantly lower in university hospitals. Loperfido et al.[17] prospectively studied the complication rates reported by small and large centres stratified by a threshold volume of 200 procedures performed annually. Small centres (i.e. <200 procedures per year) and precut technique were found to be independent risk factors for major complications overall; age <70 years, pancreatic duct opacification, and nondilated common bile duct were identified as risk factors for PEP.

Testoni et al.[18] compared high and low-volume centres (median: 257 versus 45 procedures per year) to identify the risk factors for PEP. There were more procedures of Grade 3 difficulty performed in the high-volume centres, but the PEP rates in the two centre types or according to expert and non-expert operators were not significantly different (3.8% versus 5.5%). Univariate and multivariate analyses of data from the high-volume centres found a significant association of PEP with a history of pancreatitis, young age, absence of bile duct stones, >10 attempts to cannulate Vater's papilla, pancreatic duct cannulation, and precut technique.

An Austrian nationwide voluntary benchmarking project collected data from both academic and community-based endoscopy centres. Fourteen were high-volume centres performing more than 200 procedures per year and 28 were low-volume centres with fewer than 200 procedures per year. A total of 13,513 procedures were analysed. The patient population included 36% with severe comorbidities and 26.9% on anticoagulation medications. The common bile duct was visualised in 88.7% of the procedures; nevertheless, the percentage of naïve papillae was not mentioned and nor was the difference in bile duct visualisation between low and high-volume centres. The overall therapeutic and diagnostic targets were achieved in 84.8% and 80.3%, respectively. Precut sphincterotomy was associated with an increased risk of PEP (7.9% versus 4.1% in other patients), but use of the needle knife was not. GW-assisted cannulation was used in 84.6% and PEP rates were significantly higher with this technique (4.3% versus 1.3%). High-volume centres had increased rates of bleeding and cardiopulmonary complications, but there were no differences in PEP and cholangitis rates.[19]

Perhaps surprisingly, the influence of the individual shape of the papilla is rarely questioned. Swan et al.[20] analysed 51 referred, primarily unsuccessful ERCPs. The reasons for failure included a long and mobile (floppy) papilla with a long intraduodenal segment of the common bile duct (8.29%), unstable position (9.32%), a small papilla (4.14%), or periampullary diverticulum (7.25%).

Table 1: Independent risk factors for PEP according to ESGE guidelines.[12]

Patient-related	Procedure-related
Definitive risk factors	
Sphincter of Oddi dysfunction	Cannulation attempts duration >10 minutes
Female gender	Pancreatic guidewire passages >1
Previous pancreatitis	Pancreatic injection
Likely risk factors	
Previous PEP	Precut
Younger age	Pancreatic sphincterotomy
Nondilated extrahepatic bile ducts	Biliary balloon sphincter dilation
Absence of chronic pancreatitis	Failure to clear bile duct stones
Normal serum bilirubin	Intraductal ultrasound

PEP: post-endoscopic retrograde cholangiopancreaticography pancreatitis; ESGE: European Society of Gastrointestinal Endoscopy.

ALTERED ANATOMY

For very obvious reasons, the success rate of ERCP is lower in patients with an altered upper gastrointestinal anatomy. In some patients, for example those with a Billroth II gastrectomy, ERCP can often be successfully performed using the standard technique. In other situations, the success rate can be increased with the use of overtube-assisted enteroscopy techniques. Skinner et al.[21] performed a systematic review of published articles on this issue, which included 23 relevant reports and 945 procedures. Among patients with Roux-en-Y gastric bypass, the ERCP success rate was 70%, and in patients with Roux-en-Y surgery with either a pancreaticoduodenectomy, pylorus-preserving pancreaticoduodenectomy, or hepaticojejunostomy, the ERCP success rate was 76%. In patients after Billroth II resection, the success rate of ERCP was 90%. All kinds of deep enteroscopy with either a single or double balloon, or with a spiral overtube, can be applied. Representative, prospective comparative studies are not realistic due to the characteristics of the procedure and the small number of ERCP procedures in patients with altered anatomy.

Smart, standard cannulation of the duct can also be prevented by juxtapapillary diverticula, particularly if the papilla is hidden inside. Numerous studies have been published and numerous approaches have been proposed for overcoming this anatomical obstacle. Techniques include use of biopsy forceps or clipping an approaching papilla, a forward-viewing endoscope with a cup, simultaneous use of two endoscopes, or two accessories in one scope; but a precut is effective in most difficult scenarios.

TRAINING

Everyone has the right to receive qualified healthcare, including advanced endoscopy, but this legitimate requirement can be difficult to meet. Ideally, the advanced endoscopist should undergo a fellowship programme not only in ERCP, but also in endoscopic ultrasound. This should involve more than 200 ERCPs under supervision and might take several years to complete. Nevertheless, to become fully comfortable with the procedure requires, according to the authors' experience, approximately 1,000 ERCPs; and, in order to maintain a high standard, more than 100 procedures completed annually without long intervals. Several countries have strict national control over the practice, while others have a system based, more or less, on free competition.[22] The measures of competence during training and final accreditation are poorly defined. Ekkelenkamp et al.,[23] using the Rotterdam Assessment Form for continuous self-assessment by a group of 15 trainees, documented improvement of cannulation from 36–85% after 200 procedures, and from 22–68% after 180 procedures in patients with naïve papillae. Competence should be credited on learning curves rather than on threshold numbers alone.[23]

COMPLICATIONS

ERCP is a highly demanding technique and understanding of the potential complications is a must. PEP is the most frequent harmful complication and has a frequency of 5–10% in most studies; the risk factors are shown in Table 1. In its recently published guidelines for PEP prevention, the European Society of Gastrointestinal Endoscopy recommends routine rectal administration of non-steroidal anti-inflammatory drugs (NSAIDs), keeping the number of cannulation attempts as low as possible, restricted use of pancreatic GW backup technique, and precut after the insertion of a pancreatic stent in difficult cannulations. The risk of bleeding according to a meta-analysis of 21 studies was 1.3%, with 70% of the episodes classified as mild. Besides sphincterotomy, precut technique, low-volume centres, papillary stenosis, cholangitis, coagulopathy, and recent use of anticoagulation, aspirin, and other NSAIDS do not increase risk of PEP. The rate of perforation is reported to vary from 0.1–0.6%. Risk factors include sphincterotomy, precut technique, dilation, and, particularly, B II resection. Risk factors for cholangitis, which has a rate of less than 1%, include icterus, incomplete drainage, complicated strictures, and low-volume centres. PEP and complications together serve as a surrogate criterion, as mentioned above.[24]

SUMMARY

It can be concluded that ERCP itself and its related therapeutic methods are obviously extremely effective and safe, ensuring full and sustained clinical success in more than 80% of cases. The breadth and quality of the armamentarium can satisfy most demands, and comprehensive knowledge of the complications results in their effective prevention. The procedure has reached a peak and cannot be significantly improved in

tertiary centres. Nevertheless, it remains invasive and is thus potentially hazardous when done improperly. Most of our knowledge of and experience with ERCP has been obtained from several regularly publishing centres and may be prone to bias. How then to proceed? The relevant professional societies should use their influence to organise training programmes in advanced endoscopy, respecting the needs of the patient population, local healthcare systems, and legal principles. The training and continuing education programmes must be precisely and transparently organised, allowing all trainees the opportunity to fully master the procedure before performing it on their own, and must allow qualified endoscopists to maintain their skills and expand their knowledge. To obtain representative information about what we do is a principal goal. Countries with high standards of healthcare and endoscopy should begin building a web-based, online central registry of their procedures, beginning with the leading centres. Continuing participation by community units would follow, respecting local legislation, data security, and voluntary principles. Reporting should take into account the universally accepted definitions, classifications, and terminology.

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BRIDGING PAEDIATRIC LIVER DISEASES TO ADULT CARE: WHAT DOES THE GASTROENTEROLOGIST NEED TO KNOW?

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ABSTRACT

Advances in medical and surgical therapy mean that significant numbers of children with previously fatal liver disease are surviving into adult life. In particular, 80% of transplant recipients now survive for over 20 years. Gastroenterologists and hepatologists who treat adult patients need to be aware of the clinical management and complications of diseases originating in infancy, such as biliary atresia, progressive familial intrahepatic cholestasis, Alagille syndrome, and metabolic diseases such as hereditary tyrosinemia type 1. They need to be familiar with the long-term consequences of liver transplantation in childhood, e.g. renal failure, recurrent disease, osteoporosis, and post-transplant malignancies, especially post-transplant lymphoproliferative disease, which differs in presentation and evolution from adult transplant recipients. Survivors of childhood illness require a different approach to that for young adults presenting after 18 years of age. Adult physicians need to consider the emotional, social, and sexual health of these young people, and be aware of the high rate of non-adherence, both for clinic appointments and medication, as well as the implications for graft loss, particularly after transition to adult services. Developing adequate transitional care for these young people is based on effective collaboration at the paediatric–adult interface and is a major challenge for paediatric and adult providers alike in the 21st century.

Keywords: Paediatric liver disease, liver transplantation, adolescent transition.

INTRODUCTION

Over the last 25 years there have been significant advances in medical technology and therapy that have improved the diagnosis and management of paediatric liver disease. Children with previously fatal diseases now survive into adult life in increasing numbers. In particular, the success of liver transplantation means that the survival rate for child and adolescent recipients of liver transplantation is 80% over 20 years, thus most children with liver disease can now expect to become adults.[1,2]

In our programme in Birmingham, we have transferred nearly 800 young people with liver disease or post-transplant to adult services (Table 1 and Table 2). The majority of children with liver disease had viral hepatitis, autoimmune liver disease, or cystic fibrosis (CF), while nearly 200 were post-transplant. The aim of this paper is to familiarise gastroenterologists caring for adults with the specific differences of childhood liver disease and how to manage the long-term complications both of paediatric liver disease and of liver transplantation in adult services. In particular they need to be familiar with rare diseases originating in infancy, such as biliary atresia, progressive familial intrahepatic cholestasis (PFIC),[1-4] Alagille syndrome (AGS), and metabolic diseases such as hereditary tyrosinemia type 1 (HT-1) and CF, as few of these children survived into adulthood prior to recent developments in medical and surgical management. They also need to be aware of the different phenotypes of these diseases and their multi-organ involvement, which may include cardiological, renal, and/or neurological progression, and also the risk of hepatocellular carcinoma (HCC) in all children with prolonged chronic liver disease.

Table 1: Birmingham programme: outcome of transfer to adult care 1989–2014 (n=862).

Patient category	Transferred, n	Current status	Died, n
Transplanted	236	215 alive	19
Chronic liver disease	626	10 transplanted	2
		595 alive, 2 awaiting transplant	31

Table 2: Diagnosis of 519 patients with chronic liver disease transferred to adult care in the Birmingham programme (1989–2012).

Diagnosis	Transferred, n	Alive, n	Died, n	Transplanted, n
Viral hepatitis	147	146	1	0
Cystic fibrosis liver disease	99	85	14	5 (2 died)
Autoimmune liver disease	84	82	2	2 (2 died)
Other	82	80	2	0 (1 on waiting list)
Metabolic syndrome	32	32	0	1 (1 on waiting list)
EHBA	25	25	0	1
Fatty liver disease	23	23	0	0
Alagille syndrome	11	10	1	0
Wilson's disease	9	9	0	0
A1AT deficiency	5	5	0	1
Intestinal failure	2	2	0	0

EHBA: extrahepatic biliary atresia; A1AT: alpha-1 antitrypsin.

Gastroenterologists caring for adults should also be aware of the long-term consequences of liver transplantation in childhood, e.g. renal failure, recurrent disease, osteoporosis, atherosclerosis, and post-transplant malignancies, especially post-transplant lymphoproliferative disease which may present with gastrointestinal (GI) bleeding or anaemia.[1,2] Although adult providers will be expert in managing adult liver disease pre and post-transplantation, managing young adults who have been exposed to long-term immunosuppression poses different challenges. For example, they will need to consider a different approach to young people who have survived childhood illnesses compared with young adults presenting after the age of 18 years, as those surviving childhood illness may require greater psychosocial support. As with all young adults, physicians will need to consider their emotional, social, and sexual health. They should also be particularly aware of the high rate of non-adherence both for clinical appointments and medication, and the implications for graft loss, particularly after transition. The challenge of developing adequate transitional care for these young people is based on effective collaboration at the paediatric–adult interface and is a major challenge for paediatric and adult providers alike in the 21st century.

The support of societies such as the Children's Liver Disease Foundation in the UK (www.childliverdisease.org) or the British Liver Trust (www.britishlivertrust.org.uk) may be beneficial to both patients and providers, both before and after transition.

BILIARY ATRESIA

Extrahepatic biliary atresia is a disease of unknown aetiology with no proven genetic basis. It occurs in approximately 1 in every 15,000 live births.[3] There is a syndromic or embryonic form (biliary atresia splenic malformation syndrome) in 10–20% of cases with other congenital anomalies,

such as polysplenia, situs inversus, cardiac anomalies (e.g. atrial and ventricular septal defects), and absence of the inferior vena cava.[4] The perinatal or acquired form is more common and represents 80–90% of cases. The underlying pathogenesis is unknown, but is likely to be multifactorial based on the interaction of genetic and environmental factors.[4]

Initial management is based on early diagnosis and palliative surgery, Kasai portoenterostomy, in which the biliary tree is excised to expose biliary channels, with a Roux loop being created for drainage. The operation is considered to be successful if there is restoration of biliary flow within 6 months, but is dependent on the patient's age at the time of surgery, the expertise of the surgeon, and the extent of fibrosis at operation.[4] In general, success rates are approximately 60%. Although biliary atresia is the main indication for liver transplantation worldwide and accounts for 76% of children under the age of 2 years, 80% of children who have a successful operation survive 15 years or more without transplantation.[4] There are several studies of long-term outcome following successful Kasai.[5,6] The majority of survivors have cirrhosis and portal hypertension, but have normal fertility, complete primary and secondary education, and are in employment.

Issues for Adult Providers

Adult providers need to be familiar with the aetiology of biliary atresia in which the intrahepatic ducts are malformed and there is a portoenterostomy, which means that interventional radiology, such as a percutaneous transhepatic cholangiogram, is not a feasible investigation for progressive cholestasis. They will be experienced with managing the complications of portal hypertension and biliary cirrhosis, but need to be aware of the potential for cholangitis (requiring therapeutic and prophylactic antibiotics) leading to biliary cirrhosis and the need for transplantation. In young adults with end-stage liver disease, malnutrition, fat-soluble vitamin deficiencies, and metabolic bone disease are frequent issues and should be managed using standard adult guidelines.[4,5]

ALAGILLE SYNDROME

AGS is an autosomal dominant condition with an incidence of 1 in every 100,000 live births.[7] It is a multisystem disorder with cardiac, facial, renal, ocular, and skeletal abnormalities. The condition is caused by mutations in the *JAG1* gene encoding Jagged-1, which is a ligand of Notch-1. There are many different mutations and a high frequency of sporadic cases, while <1% have mutations in the gene encoding Notch-2.[8]

Infants present with persistent cholestasis, severe pruritus, hepatomegaly, and failure to thrive that is complicated by GI reflux and severe steatorrhoea secondary to fat malabsorption or pancreatic insufficiency.[9] The characteristic facial features are difficult to identify in infancy, but are obvious in adult life. They include a triangular face with a high forehead and frontal bossing; deep, widely spaced eyes; a saddle-shaped nasal bridge; and a pointed chin. Cardiac abnormalities include peripheral pulmonary stenosis, pulmonary and aortic valve stenosis, and the tetralogy of Fallot. Skeletal abnormalities include abnormal thoracic vertebrae, 'butterfly' vertebrae, and curving of the proximal digits of the third and fourth finger. Ocular abnormalities include optic disease, papilloedema secondary to intracranial hypertension, and posterior embryotoxon. Renal disease varies from mild renal tubular acidosis to severe glomerular nephritis. Hepatosplenomegaly is unusual unless there is progressive fibrosis, which is rare. Management in childhood depends on the severity of associated extrahepatic disease and cholestasis. Intensive nutritional support with fat-soluble vitamins, especially vitamin E, is essential, and pancreatic supplements may be required. Cardiac anomalies require corrective surgery, with balloon dilatation or surgical correction of pulmonary valve or pulmonary artery stenosis.[10]

With adequate support, about 50% of children regain normal liver function without significant cholestasis by adolescence while others require liver transplantation in childhood. Overall mortality is 20–30%, due to cardiac disease or progressive liver disease.[10,11] In a study of 163 children with AGS and liver involvement, 44 (33%) required liver transplantation;[11] overall survival rates were 68% and 62% at 10 and 20 years, respectively. Catch-up growth after transplantation may occur.

Issues for Adult Providers

Issues for adult providers include management of cholestasis, pruritus, and hypercholesterolaemia with extensive xanthoma, but liver failure is rare in adult life. Young adults with significant cardiac disease may develop pulmonary hypertension or

require further surgery. Renal disease requires specific management or renal transplantation as required. Patients have a 50% chance of having an affected child and appropriate counselling is required. Although prenatal diagnosis is now possible, termination is not common because of the varied phenotype.[8]

PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS

PFIC encompasses a group of inherited cholestatic diseases caused by mutations in genes encoding the components of the hepatocellular transport system involved in bile synthesis. They are autosomal recessively inherited, and interaction with modifier genes plays a role in the severity of the clinical phenotype. Modifier genes include the apical sodium-dependent bile acid transporter and the farsenoid X receptor, a bile acid-activated transcription factor which mediates transcriptional repression of genes important in bile acid and cholesterol homeostasis. They are rare, with an incidence of 1/50,000–1/100,000, but show worldwide occurrence and equal sex distribution.

PFIC1 is caused by mutations in *ATP8B1*.[12] Benign recurrent intrahepatic cholestasis type 1 (BRIC1) is also caused by mutations in *ATP8B1* and is an allelic condition to PFIC1. It presents in the first months of life with episodes of jaundice and severe pruritus with very high serum bile-acid levels. Due to the extrahepatic expression of the *ATP8B1* gene, other clinical features include pancreatitis, diarrhoea (loss of the ileal transporter), sensorineural deafness, and short stature.

PFIC2, also known as bile salt export pump (BSEP) deficiency, is caused by mutations in *ABCB11*.[13] BRIC type 2 is also caused by mutations in *ABCB11* and is an allelic condition to PFIC2. BSEP is the major canalicular BSEP in man and extracts bile salts from hepatocytes into canaliculi. Its deficiency presents with persistent cholestasis from birth, coagulopathy secondary to fat-soluble vitamin K deficiency, and pruritus; there are no extrahepatic manifestations.[14] HCC has been reported in infancy and should be monitored with alpha-fetoprotein levels and ultrasound scans.

PFIC3, also known as multidrug resistance protein 3 (MDR3) deficiency, is caused by mutations in the *ABCB4* gene.[15] *ABCB4* encodes MDR3 that translocates phosphatidylcholine and other membrane phospholipids from the inner to the outer canalicular membrane leaflet, so that phospholipids are available for extraction by bile salts. There is variable cholestasis in this condition and it may present at any time during childhood or adult life with complications of chronic liver disease, such as portal hypertension and liver failure; pruritus is often mild.

PFIC4 has been recently described and is due to truncating mutations of the gene encoding tight junction protein 2 on chromosome 9q21.11. Truncation of the protein causes disruption of the integrity of the cholangiocyte membrane; it is probably localised only to the liver in humans. PFIC1, PFIC2, and PFIC4 have low-normal gamma-glutamyl transpeptidase (GGT) despite marked cholestasis, which is in contrast to the elevated GGT observed in PFIC3. Cholesterol tends to be low. Synthetic function is maintained until liver failure develops.

Issues for Adult Providers

Most patients require liver transplant in childhood and so, with the exception of BRIC and PFIC3, adult providers will only care for those who have survived transplantation. In young people transplanted for PFIC1, management focusses on the extrahepatic manifestations, especially diarrhoea, which is worse after transplantation and requires bile salt resins for control. Graft steatosis leading to cirrhosis and the need for re-transplant may occur.[16] Children transplanted for PFIC2 may develop recurrence due to the development of anti-BSEP antibodies and may need re-transplantation.[17] There is a theoretical possibility that female carriers of PFIC and those with milder phenotypes may become cholestatic in pregnancy.

TYROSINEMIA TYPE 1

HT-1 is an autosomal recessive disorder caused by a defect of fumarylacetoacetase. More than 40 mutations have been described,[18] and there is a high lifetime risk of developing HCC.[19]

Clinical features are heterogeneous, even within the same family. Acute liver failure is a common presentation in infants, while older children present with chronic liver disease, rickets, a hypertrophic cardiomyopathy, renal failure, or a porphyria-like syndrome with self-mutilation. Renal tubular dysfunction and hypophosphataemic rickets may occur at any age.

Table 3: Aims of transition.

1.	To provide high-quality, coordinated, uninterrupted healthcare that is patient-centred, age and developmentally appropriate, future-focussed, culturally competent, flexible, responsive, and comprehensive
2.	To promote skills in communication, decision-making, assertiveness, self-care, self-determination, and self-advocacy
3.	To enhance sense of control and interdependence in healthcare
4.	To maximise lifelong functioning and potential
5.	To support the parent(s)/guardian(s) of the young person during transition and in particular to enhance their advocacy skills

Management should be conducted with a phenylalanine and tyrosine-restricted diet and nitisinone, 2(2-nitro-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC), which prevents the formation of toxic metabolites and allows normal growth and development.[20,21] The long-term outcome of children and young adults who have HT-1 and are treated with nitisinone is unknown, but there are emerging concerns about neurocognitive function.[21]

Issues for Adult Providers

Young adults with HT-1 require long-term monitoring and follow-up with 6-monthly abdominal ultrasound and CT scans, or MRI and alpha-fetoprotein estimation, for early detection of HCC. As the metabolites are also produced by the kidney, monitoring of renal function is essential, especially in those who have been transplanted. Liver transplantation is now only indicated for the development of acute or chronic liver failure unresponsive to NTBC, or suspicion of HCC.[21]

CYSTIC FIBROSIS

CF has an incidence of 1 in every 3,000 live births worldwide.[22] The gene defect is an abnormality in the CF transmembrane conductance regulator located on chromosome 7q31. It is a multi-organ disease mainly affecting the lungs and pancreas. CF-associated liver disease occurs in 27–35% of patients and usually presents before the age of 18 years.[23] Approximately 5–10% of all CF patients will develop cirrhosis and portal hypertension during the first decade of life and present with complications in adolescence or early adult life.[24] Liver failure is a late event accounting for 2.5% of overall CF mortality.[25]

Use of ursodeoxycholic acid (20 mg/kg) may stabilise progression of disease, but there are no large randomised controlled trials. Currently, large numbers of young people have transferred to adult care (Table 2).

Issues for Adult Providers

Holistic management of CF in young adults includes:

- Standard management of pancreatic deficiency and diabetes if present
- Counselling about adolescent issues, fertility, and lifestyle. Most women are fertile, but menarche and conception may be delayed due to malnutrition and ongoing chronic disease. About 98% of males are infertile due to failure of the vas deferens and should be appropriately counselled
- Managing the combination of CF liver and lung disease, portal hypertension, and hypersplenism. This requires a multidisciplinary approach from both respiratory and hepatology teams for optimum care based on standard adult management
- Making a decision about timing for liver transplantation

The indications for liver transplantation include malnutrition unresponsive to nutritional support, intractable portal hypertension, and hepatic dysfunction. It is essential that transplantation is carried out before pulmonary disease becomes irreversible.[25] The outcome following liver transplantation is good. A number of studies have indicated good if not better initial survival, an absence of significant pulmonary complications, and stabilisation of pulmonary function and nutritional parameters, but deaths from respiratory failure in early adult life should be anticipated.[26]

POST-TRANSPLANT MANAGEMENT

The long-term survival and quality of life post-transplant are influenced by: late technical complications such as hepatic arterial or portal vein thrombosis, biliary strictures, the development

of graft hepatitis or fibrosis, recurrent disease, the side effects of immunosuppression, and adherence, especially after transition to adult care.[27]

Issues for Adult Providers

Patients require:

- Annual monitoring of graft function with regular biochemical liver function tests and abdominal ultrasound
- Screening for renal dysfunction using an estimated chromium ethylenediaminetetraacetic acid glomerular filtration rate
- Measurement of lipids, blood pressure, and glucose or HbA1c for diabetes mellitus and/or metabolic syndrome
- Weight loss or anaemia should prompt evaluation of post-transplant lymphoproliferative disorder by Epstein–Barr virus polymerase chain reaction, endoscopy, and/or abdominal CT scan[27]
- Serial protocol biopsies may indicate the presence of graft hepatitis or fibrosis, which may be a form of rejection and require an increase in immunosuppression[28]

Approximately 10% of young adults require re-transplantation for chronic rejection, mostly related to non-adherence.[28]

TRANSITION TO ADULT CARE

Transition is defined as 'a multi-faceted, active process focussed on the medical, psychosocial, and educational/vocational needs of adolescents as they move from child to adult-centred care'.[29] The aims of transition are listed in Table 3. It requires a multidisciplinary approach, good communication, support, and education for both parents and young people in order to ensure that the young person is equipped to take responsibility for their own care.

The key to successful transition is good preparation, encouraging self-management skills in the young person, and establishing joint clinics between adult and paediatric providers to provide seamless care. It is important that the young person is in good health and emotionally mature enough to move to adult services, which is usually at approximately 18 years of age, but may be later in those with learning difficulties.[29]

Non-Compliance with Therapy

Several studies have identified an increase in non-adherence to medication and hospital visits following transfer to adult clinics, leading to graft loss and the need for re-transplantation in transplant survivors.[29,30] The causes are complex and include the difficulties that young people experience in the psychosocial journey from childhood to adulthood, their need to become self-reliant, and the different approach between adult and paediatric care.[30,31]

The management of non-adherence is difficult and relies on a non-judgemental approach with efforts to improve education, social functioning, and behavioural strategies to encourage self-motivation. In order to ensure a successful transfer to adult care, it is essential to establish a transition team with key workers and trained personnel to manage the process. Support of the adolescent patient is crucial and requires a multidisciplinary approach, including a supportive adult provider.[32]

CONCLUSION

Advances in medical and surgical management have transformed outcomes for children with liver disease, meaning most survive into adult life. Adult providers should be aware of the relevant issues and understand the basis of paediatric liver disease in order to provide optimum care.

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HEPATITIS E IN EUROPE: DIAGNOSIS AND TREATMENT

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ABSTRACT

Hepatitis E virus (HEV) is a single-stranded, non-enveloped, positive-stranded RNA virus that can be classified into four genotypes with distinct geographical distributions. Several reservoirs and transmission routes have been identified. The clinical symptoms of acute hepatitis caused by the different genotypes cannot be distinguished from each other and are similar to those caused by other types of hepatitis. In developed countries, fulminant hepatitis can develop in patients with underlying (liver) disease. Chronic HEV infections are reported in immunocompromised patients and can eventually result in fibrosis and even cirrhosis. Due to the nonspecific presentation, HEV infection is often misdiagnosed. Extrahepatic manifestations, mainly neurological syndromes and renal injury, have been reported. HEV infection can be diagnosed either by serological testing or by detecting HEV RNA in serum or faeces. Acute infections normally do not require treatment, but chronic infections should be treated by reducing immunosuppressive drugs, if possible, and/or using antiviral therapy. Recently, the efficacy and safety of an HEV vaccine has been studied. This review gives an overview of the current knowledge about the virus as well as the different clinical presentations, differential diagnoses, diagnostic strategies, and treatments of this infection.

Keywords: Chronic disease, hepatitis E virus (HEV), pigs, ribavirin, solid-organ transplant, zoonosis.

HEV: GEOGRAPHICAL DISTRIBUTION AND GENOTYPES

Hepatitis E virus (HEV) was discovered in 1983 after an outbreak of unexplained, non-A, non-B hepatitis at a military camp in Afghanistan.[1] It is a positive-sense, single-stranded, non-enveloped RNA virus that belongs to the genus hepevirus in the hepeviridae family. The virus consists of four genotypes with distinct geographical distributions, and all four of which can be harmful to humans. Genotypes 1 and 2 are restricted to humans, with HEV-1 found in Asia and Africa and HEV-2 found in Mexico, Nigeria, and Chad;[2] HEV is the most common cause of acute viral hepatitis in these countries.[3] Genotypes 3 and 4 can infect humans and other mammalian species such as swine, deer, rats, and mongooses.[4] These species act as potential hosts for the virus and it can be transmitted to humans by consumption of infected animals. In pig farming regions, and within herds of domestic swine, HEV prevalences of >60% have been reported.[5] Autochthonous HEV infections in Europe, the USA, and Asia are caused by genotypes 3 and 4.

Transmission of HEV Genotypes 1 and 2

HEV-1 and HEV-2 are found in developing countries with poor hygiene. The viruses are mainly transmitted by contaminated drinking water via the faecal–oral route and large outbreaks of acute hepatitis are reported.

Transmission of HEV Genotypes 3 and 4

Faecal–oral transmission of HEV-3 is reported repeatedly in pigs and swine and is considered to represent the greatest contribution to transmission within these species.[6] Over the past few years,

several HEV cases in humans have been reported to be due to the consumption of contaminated food products. The infections were linked to the consumption of undercooked pork, game, pig liver products, and shellfish.[4] It has been estimated that HEV shed in faeces from pigs and swine indirectly leads to the contamination of irrigation and drinking water via application of manure to land, and in this way can lead to the pollution of vegetables, fruit, and shellfish.[5,7]

In developed countries, cases involving transfusion-transmitted HEV infection have been reported.[8,9] In all of these cases, the donors were infected by non-travel-associated HEV genotypes. Studies on plasma pools testing positive for HEV RNA show that blood donors are often infected with HEV without having any complaints.[10,11] Seroprevalences of HEV in Europe are nationally and even regionally varied, ranging from the lowest recorded prevalence of 4.7% among Scottish blood donors[12] to 26.7% in the Netherlands[11] and even 53% in the south-east region of France, which is the area with the highest seroprevalence among industrialised countries.[13] When we compare these data with the recorded incidence of clinically evident autochthonous HEV infection in these countries, a large subclinical or unrecognised course of infection is suggested for transfusion-related HEV infection. A recent study in south-east England shows the risk and potential dangers of transfusion-transmitted HEV in immunosuppressed patients: these infections sometimes cause long-term persistent infections and can even lead to progressive chronic liver disease.[14]

A recent case report from Germany describes a male patient who was infected with HEV by liver transplantation. The patient received an HEV-infected liver from a donor with occult HEV infection. Shortly before explantation, the patient tested negative for HEV RNA and anti-HEV antibodies. One hundred and fifty days after transplantation, serology and HEV RNA were positive. Liver cirrhosis developed within 15 months and the patient died of septic shock.[15]

CLINICAL COURSE

Acute Hepatitis

Approximately half of all patients infected with HEV-1 or HEV-2 develop clinical symptoms of the infection, whereas 67–98% of patients infected with HEV-3 or HEV-4 remain asymptomatic.[4] The clinical features of acute HEV infection caused by the different genotypes cannot be distinguished from each other. In symptomatic patients, symptoms appear after an incubation period of 2–8 weeks.[16] Patients may present with unspecific complaints such as malaise, nausea, abdominal pain, vomiting, and anorexia. At presentation, patients can have fever and 40% present with jaundice.[17] During physical examination, right upper quadrant tenderness and hepatomegaly may be found. Laboratory findings show an increase in alanine aminotransferase (ALT) more than aspartate aminotransferase, as well as elevated bilirubin, alkaline phosphatase, and gamma-glutamyltranspeptidase.[18] ALT levels are sometimes normal during the period of viraemia.[19]

In highly endemic regions where patients are infected with HEV-1 or HEV-2, symptoms are most frequently observed in youths and adults.[20] In these areas, pregnant women have an especially greater risk of developing a more severe, acute liver disease that can lead to fulminant hepatic failure and even death.[21] It is suggested that this is due to differences in hormonal and immunological factors.[21,22] This epidemiological picture in pregnant women has not been observed in developed countries with predominant infection with HEV-3.

In developed countries, immunocompetent individuals without underlying diseases rarely present with symptoms. Studies into seroprevalence among blood donors underline the fact that patients are often silently infected.[10,23] Patients with symptoms are most often middle-aged and elderly males. The reason(s) for these associations are not fully understood. One explanation might be that all individuals are evenly exposed to HEV but that older patients have more significant comorbidities than young individuals and that this results in symptomatic HEV.[24] Alcohol consumption is also an important risk factor in the clinical expression of the infection. Consumption of at least 22 units of alcohol per week is strongly associated with symptomatic HEV.[25]

Several studies have shown that patients with underlying liver diseases have a poor prognosis when infected with HEV.[26] HEV infection in these patients can cause liver decompensation and acute-on-chronic liver failure.[27] One-year mortality rates of up to 70% have been reported.[4]

Chronic Infection

Chronic HEV infections, defined as the presence of HEV RNA in serum or stools for >6 months, are rarely seen in otherwise healthy patients but are increasingly being reported in immunosuppressed patients. Patients receiving solid-organ transplants (SOTs) require lifelong immunosuppressive therapy to prevent graft rejection and are prone to developing chronic HEV due to their suppressed immune system.[28] Since 2008, increasing numbers of chronic HEV infections have been reported in patients with liver, kidney, and heart transplants.[4] A recent study showed that predictive factors associated with chronic HEV infection were the depth of immunosuppression, the use of tacrolimus rather than cyclosporine A, low platelet and serum creatinine count at diagnosis, and low CD2, CD3, and CD4-positive cell counts.[29] In addition, mTOR inhibitors such as rapamycin and everolimus have a direct stimulatory effect on HEV replication by blocking the antiviral signalling pathway.[30] However, mycophenolate mofetil has been shown to have a protective effect in the clearance of HEV *in vitro*.[31] Mycophenolate mofetil probably exerts antiviral effects by inhibiting inosine monophosphate dehydrogenase, an enzyme that is important for RNA synthesis.[31]

In SOT patients it has been observed that viral clearance is either achieved within 3 months after infection or after 6 months and later. This implies that, in SOT patients, a chronic HEV infection can be defined as persisting HEV replication beyond 3 months after infection.[32] Approximately 60% of SOT recipients exposed to HEV develop a chronic infection.[29] Recipients of allogeneic hematopoietic stem cell transplantation (alloHSCT) are also at risk of developing chronic HEV due to insufficient lymphocyte recovery and the use of immunosuppressive therapy.[28,33] Studies into the seroprevalence of HEV among patients infected with HIV report conflicting results. Studies in Spain report a higher seroprevalence in patients infected with HIV,[34,35] whereas other reports found a similar seroprevalence in HIV-infected and control groups.[36-38] Chronic infections are rarely observed in HIV-infected patients, which may be explained by a high coverage of combined antiretroviral therapy in HIV-infected patients preventing a strongly decreased immune response.[16,36]

Patients with cancer who receive radiation therapy and/or immunosuppressive drugs are prone to develop clinical features of acute HEV infection, but usually recover completely following cessation of immunosuppressive treatment.[28] Chronic HEV infection can eventually progress to fibrosis and even cirrhosis, which can lead to death due to liver decompensation.[29,39,40] Cirrhosis due to chronic HEV sometimes requires re-transplantation in liver transplant recipients. These patients are at high risk of developing a recurrent infection if viral clearance is not achieved before transplantation.[40] No chronic infections with HEV-1 or HEV-2 have been reported in the literature.

HEV INFECTION MIMICS OTHER CONDITIONS

Drug-induced liver injury (DILI) is common and occurs frequently in the elderly population, as does autochthonous HEV infection. The clinical presentation of DILI is diverse and nonspecific. In order to effectively diagnose DILI, there needs to be a temporal relationship between the onset of drug therapy and biochemical evidence of liver injury. After inducing treatment with chemotherapy or other immunosuppressive drugs, infection with HEV can become symptomatic and may easily be mistaken for DILI. In fact, a study among patients with criterion-referenced liver injury showed that 13% of the patients who met the criteria had autochthonous HEV infection.[41]

In alloHSCT recipients, liver dysfunction related to graft-versus-host disease (GvHD) is common. A retrospective cohort study comprising 328 alloHSCT patients showed an incidence of 2.4% for HEV infections following transplantation.[33] The presentation of liver enzyme abnormalities in these two conditions are overlapping. It is important to differentiate HEV infection from GvHD because of opposing therapeutic strategies: increment of immunosuppression in GvHD versus reduction of immunosuppression in HEV infection.

The elevation of serum transaminase levels in HEV infection is also difficult to distinguish from patients with acute liver transplant rejection. Histological features of HEV include both cholestatic and classic types of acute viral hepatitis. However, lymphocytic destructive cholangitis has also been described, which can also be seen in primary sclerosing cholangitis, drug-induced hepatitis, acute rejection, and GvHD.[42] This makes it difficult to differentiate HEV from these diseases.[43] Until now, no specific HEV-related tissue markers have been available.

EXTRAHEPATIC MANIFESTATIONS OF HEV

Neurological manifestations have been reported in both HEV-1 and HEV-3 infections. Guillain–Barré syndrome and brachial neuritis are most frequently described.[44] Other neurological disorders include transverse myelitis, cranial nerve palsies (Bell's palsy), seizure, intracranial hypertension, acute meningoencephalitis, and neuralgic amyotrophy.[4,44] Impaired renal function has also been linked with HEV infection. Both HEV-1 and HEV-3 can cause glomerular disease. A study of HEV-related glomerulonephritis in SOT patients found that the majority of patients had cryoglobulinaemia, which became negative after HEV clearance. This leads to the hypothesis that cryoglobulinaemia plays an important role in HEV-associated renal injury.[45]

DIAGNOSTICS

HEV infection can be diagnosed either indirectly by the demonstration of anti-HEV antibodies or directly by detecting HEV RNA using a (quantitative) reverse transcription polymerase chain reaction ([q]RT-PCR) in serum/EDTA-plasma or stool samples.[46] After an incubation period of 2–8 weeks, HEV-specific immunoglobulin (Ig)M usually becomes detectable in immunocompetent individuals. At the time of clinical presentation, HEV IgM has already peaked and persists in blood for 8 weeks. Huang et al.[47] found that anti-HEV IgG can be detected in all HEV-infected patients, and in 95% of patients it is already present at the time of first presentation. Anti-HEV IgG reaches peak levels at around 4 weeks after onset of symptoms, and stays positive in high levels for >1 year.[47]

The presence of anti-HEV IgM antibodies represents an acute HEV infection in immunocompetent patients and is used as a marker for acute HEV infections. The presence of anti-HEV IgG alone is a marker of past infection. However, patients can also be re-infected with HEV. This is represented by a rapid increase in IgG titres, with HEV RNA becoming detectable by RT-PCR.

There has been poor correlation between the results of some immunoassays for the detection of anti-HEV IgM/IgG in terms of sensitivity, specificity, and agreement of results. Specificity levels range from 78.2–95.6% and sensitivity levels range from 72–98%, depending on the assay used;[48] the Wantai test is frequently used in Europe but was not evaluated in this study. We found that this assay is more specific (specificity: >99%; sensitivity: 75%)[49] than the tests investigated by Drobeniuc et al.[48] Our study also showed that, even though most assays are based on the detection of antibodies directed against HEV-1, there is major cross-reactivity against HEV-3, confirming that there is one serotype of HEV and contradicting earlier speculations that this may be the cause of the lower sensitivities of HEV-1 based immunoassays.

Due to the impaired immune responses and bad performance of IgM assays in immunocompromised patients, it is recommended to use real-time RT-PCR to detect HEV RNA in these patients. The virus is detectable in the blood of immunocompetent patients during the incubation period and in the early symptomatic phase, and in faeces 1 week before the onset of clinical signs.[50] A few days to weeks after the onset of clinical symptoms, HEV RNA is cleared from the blood; however, the virus continues to be shed in stools for another 2 weeks.[51] In patients developing chronic HEV infection, HEV RNA in serum remains detectable. Real-time qRT-PCR is also useful for monitoring treatment efficacy.

TREATMENT

In immunocompetent patients, acute HEV infection does not normally require treatment. There is one report describing the treatment of a 61-year-old man who had severe acute HEV-3 infection, which was treated with ribavirin. Liver inflammation rapidly improved concurrently with a decrease in HEV RNA levels after starting treatment. Prospective studies are needed to evaluate the role of treatment with ribavirin in patients with severe acute HEV infection.[52]

SOT patients treated with immunosuppressants to prevent rejection are at high risk of developing chronic HEV infection. Besides their primary inhibition of T cell proliferation, immunosuppressants can also affect the function of other types of immune cells, including B cells, dendritic cells, and natural killer cells. Suppression of the immune response in this way prevents the elimination of viral infections.[53] Given the strong association between immunosuppressant use and chronic HEV infection, dose reduction or even withdrawal of immunosuppression, if possible, is considered to be the first step in the treatment of HEV infection. In a retrospective study among 85 SOT recipients infected with HEV, nearly one-third achieved viral clearance after immunosuppressant dose reduction alone.[29]

Reduction of immunosuppressive therapy targeting T cells, such as cyclosporine A and tacrolimus, has a particularly great impact.[29] However, in heart and lung transplants this strategy should be considered with more caution given the difficulty in monitoring rejection in these patients.

In patients who fail to eliminate the virus after reduction of immunosuppressive drugs, and in those whose dose of immunosuppressive drugs cannot be reduced, antiviral therapy should be considered. Antiviral therapy consists of the off-label use of pegylated interferon alpha or ribavirin therapy, or a combination of both. Pegylated interferon therapy has been reported in a couple of studies with small populations consisting of 1–3 patients.[54-56] A 3-month course of pegylated interferon therapy showed sustained HEV clearance in two liver transplant patients[54] and one haemodialysis patient.[55] In one liver transplant recipient there was a relapse after completion of treatment. A 12-month course of pegylated interferon therapy showed sustained viral clearance in one patient.[56] However, interferon therapy cannot be used in patients with heart, kidney, and lung transplantation due to the increased risk of acute rejection. For these patients, and for patients with chronic HEV who are not able to clear the virus, ribavirin seems to be an efficient treatment option.

The largest study evaluating the effect of ribavirin therapy in SOT patients was conducted among 59 patients in France.[57] Kamar et al.[57] found an overall sustained virological response (SVR) in 78% of the patients. Six of the ten patients who had a recurrence were retreated, with four of them having an SVR after completing the second course of ribavirin. Ribavirin was administered for a median of 3 months and there was no difference in the overall rate of SVR between patients who received ribavirin for ≤3 months and those who received it for >3 months. Therefore, the authors suggest that ribavirin therapy for a duration of 3 months is sufficient.[57] The main side effects of ribavirin were anaemia and impaired renal function. Debing et al.[58] detected a mutation in the viral polymerase encoded by the HEV RNA of two non-responders to ribavirin treatment. This G1634R mutation seems to increase the replicative capacity of HEV in the liver and in this way reduces the efficacy of ribavirin.[58] Future studies are needed to investigate the clinical importance of this mutation in relation to other patient and virus-related factors in therapy resistance.

VACCINATION

Since rapid diagnostic tests for HEV infections are not yet readily available in most countries, a safe and effective vaccine is highly desirable. Currently, two vaccines against HEV seem to be effective: the recombinant protein (rHEV) vaccine and the HEV239 vaccine. The safety and efficacy of the rHEV vaccine was evaluated in a Phase II study among healthy, seronegative adults in Nepal. After two doses the vaccine efficacy was 85.7%, and was 95.5% after three doses.[59] However, the vaccine's production and further clinical trials were stopped due to economic reasons. The HEV239 vaccine showed a slightly higher vaccination efficacy. The vaccine was administered to 112,604 individuals, both seronegative and seropositive, in a Phase III trial. After three doses the vaccine efficacy was 100%. The vaccine was effective against HEV-1 and HEV-4.[60] A long-term follow-up study concerning this vaccine showed an efficacy of 86.8% after 4.5 years.[61] The HEV239 vaccine has also recently been shown to be highly immunogenic in rabbits.[62] These findings make it conceivable to study the effectiveness of this vaccine in preventing HEV transmission in pig populations and to tackle the problem at the source. However, this vaccine is currently only available in China and has not been introduced in Europe yet. Future studies are required to determine the efficacy of these vaccines against HEV-3 and their safety among immunocompromised patients and patients with chronic liver disease.

FUTURE PERSPECTIVES

In developing countries, improvement in sanitary hygiene is the most important way to control the faecal–oral transmission of HEV. In industrialised countries, the main source of the infection is from domestic swine, and its impact is highest in immunocompromised patients. Future studies are needed to investigate the best approach to the problem, either through primary prevention by tackling HEV at the source and/or through secondary prevention by vaccinating high-risk patients.

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UPCOMING EVENTS

2016 Gastrointestinal Cancers Symposium

21st–23rd January 2016

San Francisco, California, USA

This symposium aims to provide an 'insight on novel mechanisms and precision care' in gastrointestinal cancers. The rich programme includes a variety of sessions, from innovative screening techniques, to controversies in screening and staging in colorectal cancer. Furthermore, surveillance for upper-gastrointestinal cancers and immunology are just a snippet of what is to come in the important key-note lectures.

18th Düsseldorf International Endoscopy Symposium

11th–13th February 2016

Düsseldorf, Germany

The Düsseldorf International Endoscopy Symposium presents the latest developments in endoscopic imaging and minimally invasive approaches to gastrointestinal and biliopancreatic diseases. The management of gastrointestinal cancers in relation to endoscopy is, unsurprisingly, a recurring theme in the programme, but is also accompanied by an update on the state of the art in endoscopy technology, and a selection of satellite symposia.

11th European Crohn's And Colitis Organisation Congress of Inflammatory Bowel Diseases 2016 (ECCO 2016)

16th–19th March 2016

Amsterdam, Netherlands

Alongside its strong educational programme, ECCO 2016 features cutting-edge scientific research surrounding future therapies for the treatment of inflammatory bowel disease (IBD). The congress includes a variety of international specialists, each working at the forefront of research in cell therapy, genetic testing and its application, and immunological research, such as the effect of viral infection on the development of IBD, and much more.

3rd Annual Digestive Diseases: New Advances

1st–2nd April 2016

Philadelphia, Pennsylvania, USA

This congress promises to present a comprehensive and complete overview of the current landscape of treatment for physicians, nurses, physician's assistants, and carers working in the complex field of gastroenterology. With a focus on some of the biggest issues facing gastroenterologists, such as gastroparesis, hepatitis B and C, and oesophageal cancers, one can expect to leave the event feeling considerably more knowledgeable.

Gastro Update Europe

29th–30th April 2016

Prague, Czech Republic

Following the success of last year's Gastro Update Europe, this young, yet rapidly growing congress is returning once again with a programme detailing the most significant and up-to-date developments in gastroenterology. Join expert speakers and leading researchers as they comprehensively cover each medical discipline, discuss the practical relevance of study results, and much more. This meeting aims to foster the gastrointestinal knowledge of each attendee.

Digestive Disease Week® (DDW) 2016

21st–24th May 2016

San Diego, California, USA

With over 15,000 physicians, researchers, and academics in attendance at DDW 2015, this congress is now considered to be the largest and most prestigious global event in the field of gastroenterology. Expect outstanding educational sessions and pioneering research in areas within gastroenterology, hepatology, and endoscopy, to mention but a few, as well as plentiful networking and social opportunities throughout the week.

33rd World Congress of Internal Medicine (WCIM Bali 2016)

22nd–25th August 2016

Bali, Indonesia

Bali, 'The Island of the Gods', is a stunning location for this congress, whose goal is to promote scientific knowledge, medical advancement, and the delivery of effective healthcare in internal medicine. Each day, the extensive scientific schedule, which includes a wealth of workshops, courses, and presentations on gastroenterology, will be followed by sensational traditional performances and cultural experiences that cannot be missed.

United European Gastroenterology (UEG) Week 2016

15th–19th October 2016

Vienna, Austria

Despite being nearly a year away, UEG Week 2016 is already in EMJ's diary. Not just the sheer size of the event, which last year attracted over 13,200 delegates from 118 countries, but also the fantastic quality of the gastroenterological information disseminated, make this congress one of the most important of the year for anyone involved in the field of gastroenterology. The scientific programme is set to include presentations on the most recent advances in clinical management, discussions on up-to-date research into gastrointestinal and liver disease, and several types of fascinating symposia and forums. The aim of the meeting is to enable those in attendance to connect, to share and advance scientific knowledge, and ultimately to improve patient outcomes for those with gastroenterological disorders.