TREATMENT STRATEGIES
GASTROENTEROLOGY

Volume 4 Issue 1

- Hepatic Encephalopathy
- Helicobacter Pylori
- Diverticulitis
- Hepatitis

Includes a Review of the 23rd UEG Week 2015 - Barcelona

Robust protection against recurrent episodes of hepatic encephalopathy (HE)[1]

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6-month data

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XIFAXAN® 550 is indicated for reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥ 18 years of age.[4]

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The Cambridge Research Centre

Managing Director **Nigel Lloyd**
nigel@cambridgeresearchcentre.co.uk
Publishing Director **Sara Smith-Jones**
sara@cambridgeresearchcentre.co.uk
Commissioning Editor **Libby Cooper**
libby@cambridgeresearchcentre.co.uk
Sales and Advertising **Steve Bishop**
Filming **Martin Janes**
video@cambridgeresearchcentre.co.uk
Credit Control Manager **Emma Jones**
emma@cambridgeresearchcentre.co.uk
Accounts **Vipul Patel**

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The Cambridge Research Centre
info@cambridgeresearchcentre.co.uk
www.cambridgeresearchcentre.co.uk

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Welcome... to the latest edition of *Treatment Strategies - 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. Alongside this we bring you a selection of reviews, and some groundbreaking peer-reviewed research.

Over 13,000 specialists, experts, and students descended upon Barcelona for the biggest UEG Week yet, and the TS Series 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 WHO's new classification of processed meats as carcinogens.

This eJournal also includes a number of captivating papers that summarise some of the most influential research from this year. Cuomo *et al*. present the latest in the management of diverticulitis and how to best prevent recurrence with a unique look at the complex evaluation methods required. We have a report of the Norgine-supported sumposium on advanced chronic liver disease. Alongside these we have many other cutting-edge papers, containing content that we hope will aid you in your current work.

As we come to the end of another great year, we would like to thank you, our readers, for your ongoing support and interest. We would also like to extend our thanks to our editorial board, who provide an invaluable service. A special mention also to Jordi Estruch from United European Gastroenterology for allowing us the use of his tremendous photos.

We hope that Treatment Strategies Gastroenterology can provide you with the best new information for your practice and we look forward to seeing you in Vienna for UEG Week 2016.

Nigel Lloyd, Managing Director

The Cambridge Research Centre wishes to thank the following societies for their assistance and involvement in this publication.

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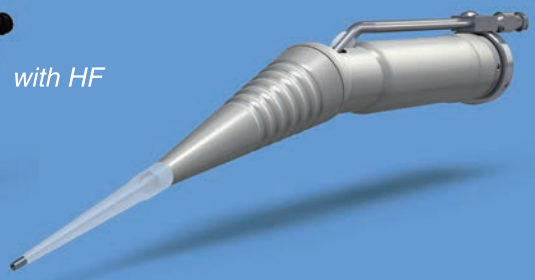

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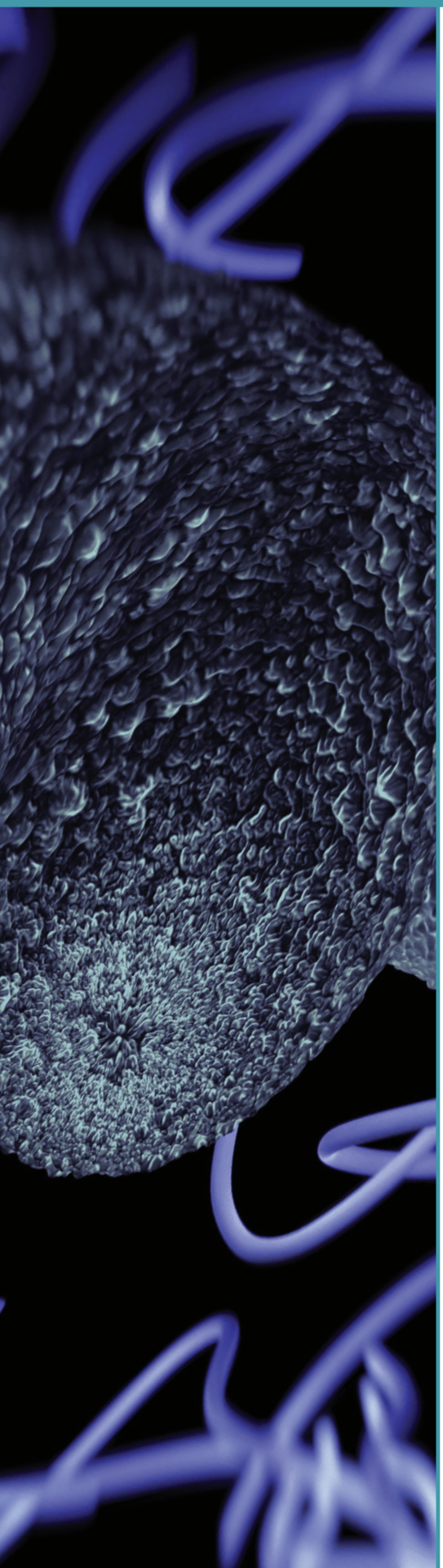

CHRONIC LIVER DISEASE

A SLOW, SILENT, BUT PREVENTABLE DEATH

According to the World Health Organization, in 2008, 47.147 Europeans died of liver cancer, and 84.697 Europeans died of liver cirrhosis. These figures combined exceeded breast cancer mortality figures (103,255)[1].

Worldwide, both cirrhosis and liver cancer are on the rise.

THE CAUSES

The major causes of chronic liver disease are:

- Lifestyle (alcohol and overweight/obesity, leading to alcohol- or non-alcohol related fatty liver disease)
- Virus infection (mainly viral hepatitis B and C), and
- Genetic factors including autoimmune diseases

In addition, alcohol consumption by those who are infected with chronic hepatitis B and/or C multiplies the risk of developing cirrhosis and primary liver cancer[2].

ON THE POSITIVE NOTE, THE VAST MAJORITY OF CHRONIC LIVER DISEASE CASES CAN BE PREVENTED AND/OR TREATED

With the recent publication of its manifesto[3], ELPA calls on policymakers to ensure that an integrated approach, from prevention, to early diagnosis of a possible liver problem (e.g. via enzyme testing), to treatment, is taken to deal with the growing burden of liver disease.

ABOUT ELPA:

ELPA emerged from a desire among European liver patient groups to share their experiences. In June 2004, 13 patient groups from 10 European and Mediterranean Basin countries met to create the association. ELPA which formally launched in Paris, on April 14th 2005, now has 29 members from 24 countries.

ELPA and its members are dedicated to multi-level initiatives involving EU and national policymakers, liver specialist associations and public health experts.

European Liver Patients Association

ELPA

For more information about ELPA, please visit our website at **www.elpa-info.org** or contact:

Margaret Walker, CEO
Mobile number: +41 79 778 30 19
E-mail: margaret@elpa-info.org

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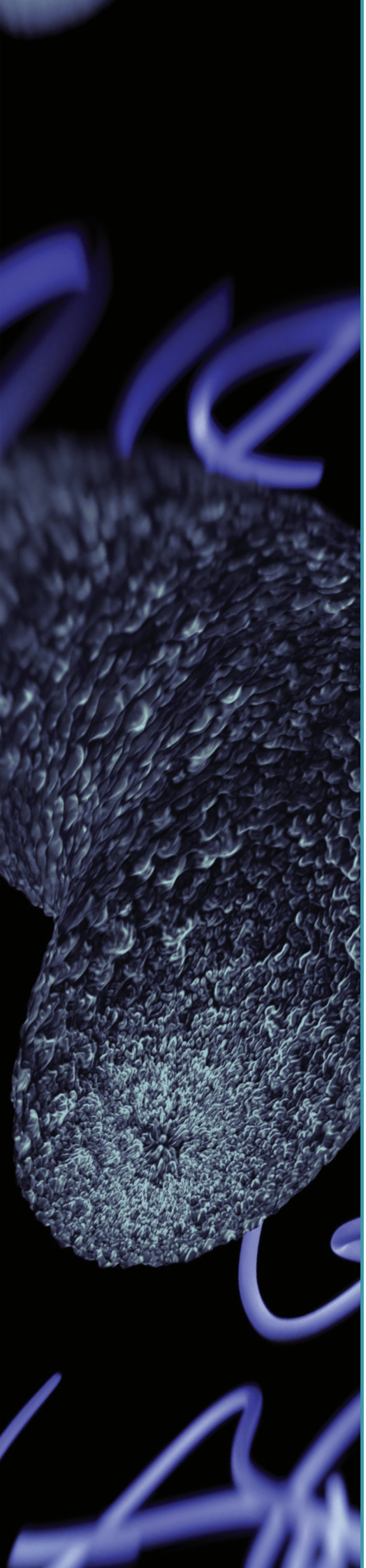

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UEG Week 2015

24th - 28th October 2015 - Barcelona

A Review of the 23rd United European Gastroenterology Week

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Attracting more than 13,000 researchers and clinicians, UEG Week 2015 in Barcelona was incredibly successful and provided a great deal of exciting new data to discuss and inspire.

Among the most innovative new data were colonoscopic perforation outcomes following endoscopic procedures in the largest European case series, how a novel method for studying pancreatic phenotypes of cystic fibrosis *in vitro* can help tailor drug screening, and the role of somatic mutations in Toll-like receptor 4 signalling alterations in oesophageal cancer. There was also the finding that maintenance treatment with ozanimod (a sphingosine 1-phosphate receptor modulator) increases the likelihood of clinical remission versus placebo in moderate-to-severe ulcerative colitis and the discovery that segment length, low-grade dysplasia and age at diagnosisare predictive of progression to cancer in Barrett's oesophagus.

There was some promising news for patients with inflammatory bowel disease. For the first time, the anti-interleukin-12 antibody, ustekinumab, was shown to benefit those with moderate-to-severe Crohn's disease failing conventional (not just anti-TNF-α) therapy. Results for another monoclonal antibody, vedolizumab, demonstrated the benefits of treatment for refractory disease in a real-life setting.

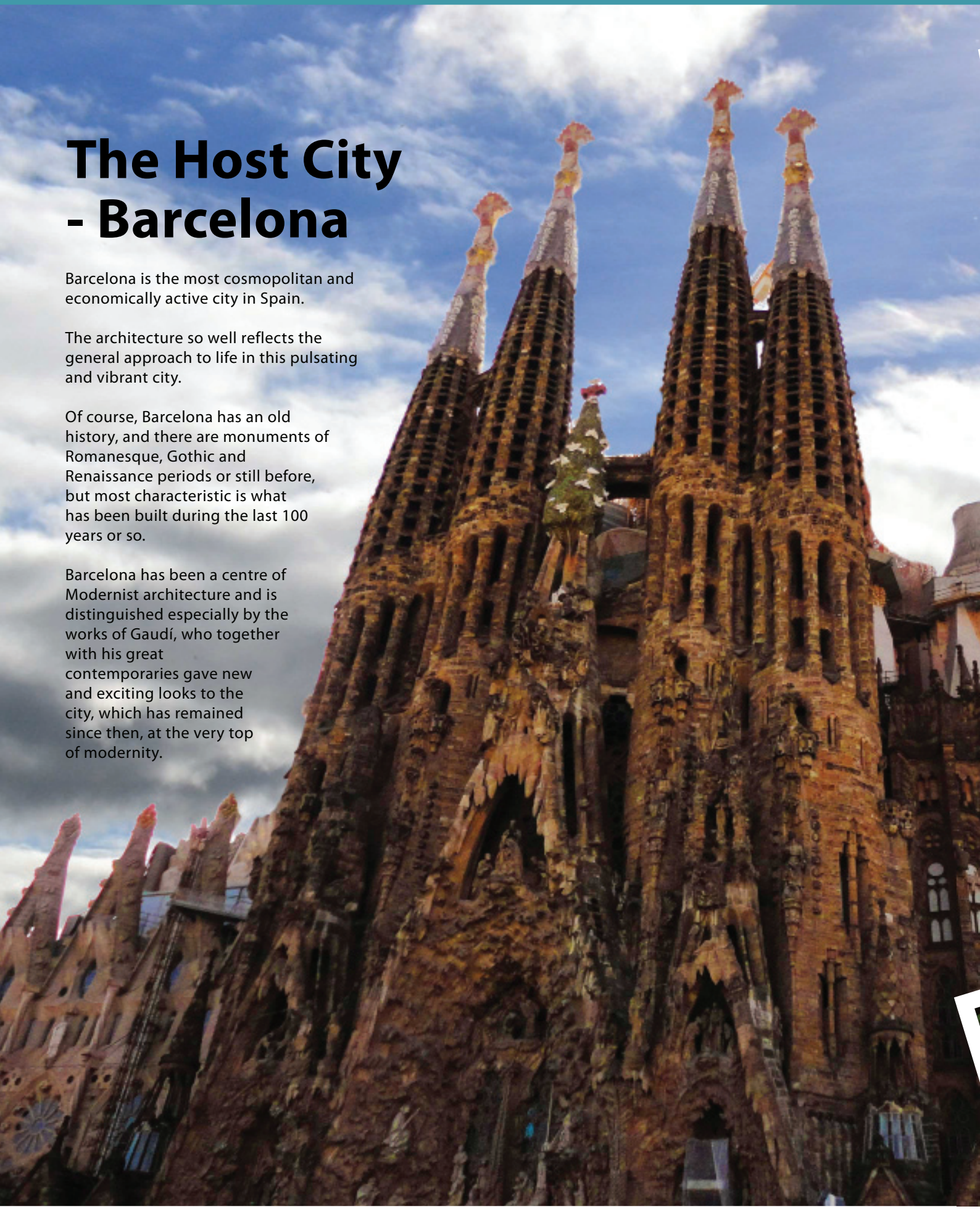
The Host City - Barcelona

Barcelona is the most cosmopolitan and economically active city in Spain.

The architecture so well reflects the general approach to life in this pulsating and vibrant city.

Of course, Barcelona has an old history, and there are monuments of Romanesque, Gothic and Renaissance periods or still before, but most characteristic is what has been built during the last 100 years or so.

Barcelona has been a centre of Modernist architecture and is distinguished especially by the works of Gaudí, who together with his great contemporaries gave new and exciting looks to the city, which has remained since then, at the very top of modernity.



As the capital of Catalonia and the second largest city in Spain, Barcelona was well-prepared to welcome UEG Week 2015 attendees back to the shores of the Mediterranean. Barcelona is a city of culture, knowledge, creativity and innovation, and delegates had plenty of opportunities to enjoy this beautiful setting.

In addition to its culture, Barcelona is the home of several world-renowned universities and hospitals, including the University of Barcelona, Hospital del Mar, University Hospital Clínic de Barcelona and the Centre for Research in Environmental Epidemiology (CREAL), which has research programmes relevant to lung physicians, including their programmes on respiratory, cancer, childhood and air pollution. The city's academic excellence makes Barcelona the perfect location to drive forward respiratory science and healthcare.

Barcelona is also one of the world's leading centres for world-class meetings, such as the UEG Week, as well as for tourism, economics and sports. Its influence in science, commerce, education, entertainment, media, fashion and the arts all contribute to its current status as one of the world's major global cities.

Moreover, Barcelona is also a key transport hub. Barcelona international airport handles over 35 million passengers per year, and the city has an extensive motorway network and high-speed rail connections. These networks ensured that congress delegates could quickly and efficiently travel to the city for 5 days of active discussion and lively interaction.

...UEG Week 2015

New therapeutic options in neurogastroenterology and motility – areas that affect many patients but with few available treatments – also appear promising. Symptomatic benefits were demonstrated for the selective 5-hydroxytryptamine4 receptor agonist, prucalopride, and the peripherally-acting mu-opioid receptor antagonist, naloxegol.

There was fascinating new evidence of a beneficial effect of a probiotic on comorbid depression and brain emotional reactivity in patients with irritable bowel syndrome. Specific microbes also appear to benefit patients with ulcerative colitis: certain bacterial signatures present after faecal microbiota transplantation are linked to a sustained response to treatment.

"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"

UEG Week 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 t he 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.

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

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 installment with much anticipation.

Faecal Microbiota Transplantation now Available in Capsule Form

A new capsule form of faecal microbiota transplantation (FMT) has raised hopes that this effective treatment for Clostridium difficile (C. difficile) infection and other bowel conditions might soon become mainstream.

A recently-reported study confirmed that capsules containing a frozen suspension of faecal material harvested from healthy unrelated donors was well tolerated and effectively resolved diarrhoea in 90% of patients with difficult-to-treat C. difficile infection.[1] Professor Antonio Gasbarrini (right) from the A. Gemelli University Hospital in Rome, Italy believes that an oral formulation that simplifies FMT is a major step forward. "FMT is an excellent treatment for C. difficile infection, but traditional methods are time-consuming and technically challenging," he says. "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."

"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"

C. Difficile Infection Challenges

C. difficile infection is a type of bacterial infection that causes severe diarrhoea, intestinal inflammation and cell death. The infection is spread via the ingestion of spores, which are passed out of the body in the faeces and can survive for many weeks or months. Standard therapy for C. difficile infection includes the use of antibiotics, however, around one-third of individuals will have a recurrent infection and many of these will have multiple recurrences.[2] The consequences of recurrences of C. difficile infection can be severe, resulting in life-threatening illness and frequent hospitalisations.

FMT in C. Difficile Infection

FMT from a healthy donor to an individual with C. difficile infection can restore the healthy gut microbiota and resolve symptoms. FMT has traditionally been performed using a liquid suspension of faeces from a related donor, which is transplanted into the body using a nasogastric tube, endoscopy, enema or colonoscopy. A recent systematic review of the literature concluded that FMT was both effective and safe for the treatment of recurrent C. difficile infection,[2] yet many hospitals have failed to embrace the technique or offer it as a potential treatment option.

"We believe that FMT is an excellent therapeutic option for patients who have failed to respond to antibiotic treatments or who have severe or multiple recurrences," said Prof. Gasbarrini. "Traditional routes of administration all have their drawbacks, so we are excited by the prospect of a capsule formulation."

In the recently-reported study of an FMT capsule, researchers in the US recruited 20 patients with C. difficile infection who had either failed to respond to antibiotic medications or had been hospitalized at least twice as a result of severe symptoms.[1] The capsules were prepared using frozen liquid stool samples from carefully screened unrelated donors and administered to the patients on two consecutive days. After the first 2 days of treatment, 14 of the 20 patients (70%) experienced a resolution of their symptoms and remained symptom free for 8 weeks. After a second course of treatment, four of the remaining patients became symptom free, resulting in an overall 90% rate of symptom resolution.

"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," said Prof. Gasbarrini.

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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).

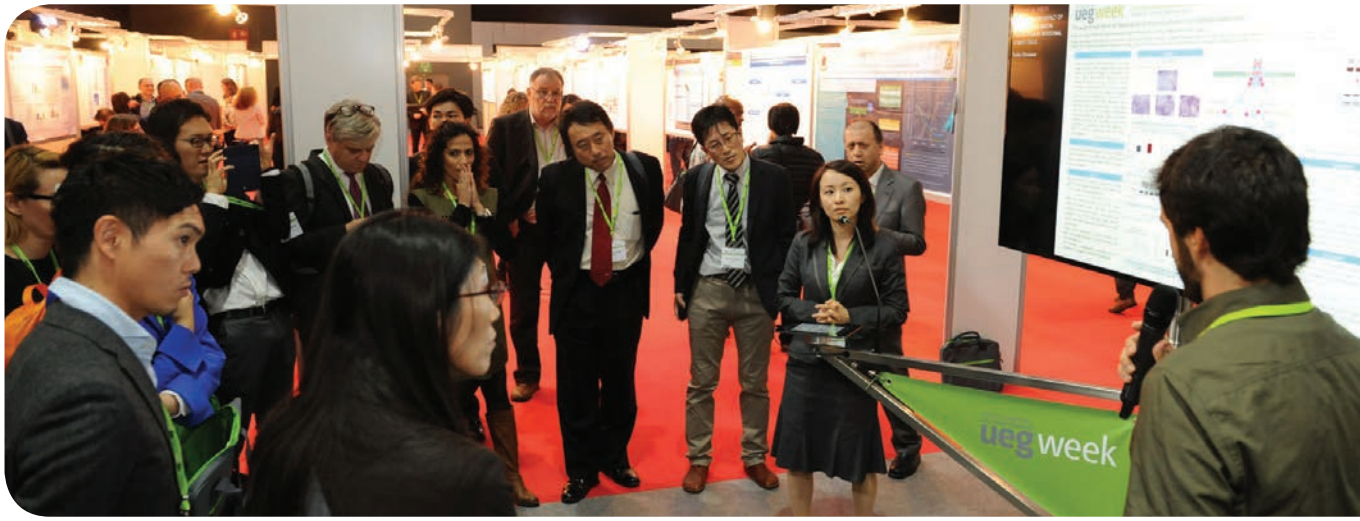
NGS allows an analysis of genes and any differences that a patient or population harbour compared with the general population. This can be applied to colorectal cancers (CRCs), which come in a number of forms, as each form has a number of associated genes. Identification of these genes can define diagnosis 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.

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 singlenucleotide 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.



Improving Risk Profiling is Key to Preventing Many GI Cancers

Cancers of the gastrointestinal (GI) tract continue to exert their toll across Europe, with many diagnosed too late for effective treatment. Bowel cancer screening programmes are now underway in most European countries, but screening for other GI cancers is patchy and not necessarily well-targeted. Experts at United European Gastroenterology (UEG) call for better risk profiling for all GI cancers in order to develop more targeted approaches to their screening and prevention.

"Our growing understanding of the causes of these cancers, coupled with new diagnostic techniques, mean we are in a good position to start developing precision prevention programmes," said Professor Rebecca Fitzgerald (right) from Addenbrooke's Hospital and the University of Cambridge in the UK, speaking at UEG Week 2015 in Barcelona. "These would ensure we triage individuals based on their relative risk and apply the most appropriate screening, prevention and treatment options to each individual."

Precision Prevention of Oesophageal Cancer

Prof. Fitzgerald and colleagues have recently applied the principles of precision prevention to the most common type of oesophageal cancer, known as oesophageal adenocarcinoma.[1] This cancer is usually found in the lower part of the oesophagus, and is often associated with gastro-oesophageal reflux disease (GORD) and its complications. The incidence of oesophageal adenocarcinoma has risen alarmingly over the past few decades, and despite treatment improvements, around half of all patients still die within a year of diagnosis.[1]

"We know from studies in the US that only about 7% of people with oesophageal adenocarcinoma are detected using current screening approaches," explains Prof. Fitzgerald. "Our theory is that we are taking the wrong approach to screening and preventing this type of cancer and we are proposing a new approach to risk stratification that could be applied to other GI cancers."

A Five-tier Strategy

According to Prof. Fitzgerald's new five-tier model of precision prevention, screening and preventative approaches for oesophageal adenocarcinoma would differ according to absolute risk.[1] People at the lowest risk levels (levels 1 and 2) would be encouraged to make lifestyle changes to reduce their risk, with primary care physicians assessing demographic risk factors (e.g. age, sex and race), recurrent reflux symptoms, family history and potential biomarkers in the blood and/or urine. Non-invasive techniques for oesophageal tissue sampling (such as Cytosponge™) and additional biomarker and genetic analyses would be applied in primary care to those at risk level 3, while secondary care endoscopy would be reserved for screening only those at risk level 4. At the highest risk level (level 5), patients would be referred to, and managed in, tertiary care.

"If this protocol was applied on a population-wide basis, it would include many at-risk individuals who are not covered by current screening practices," said Prof. Fitzgerald. "Stratifying risk in this way and applying risk-appropriate screening and prevention options would be cost-effective and detect many more cases of oesophageal cancer in their early stages."

"OMICs" and Genetic Analysis

New methods of predicting the risk of, and identifying, different GI cancers are currently being evaluated and could help to inform precision prevention models such as the one proposed by Prof. Fitzgerald. Genetic analysis is already used to predict risk in several different types of cancer, and scientists have recently found a cluster of genetic mutations that help to predict the risk of Lynch syndrome (also known as hereditary non-polyposis colorectal cancer).[2] Metabolomics, which analyses body fluids and tissue samples for particular chemicals, is a relative new technique that also looks promising for the detection of stomach cancer.[3]

"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," said Prof. Fitzgerald.

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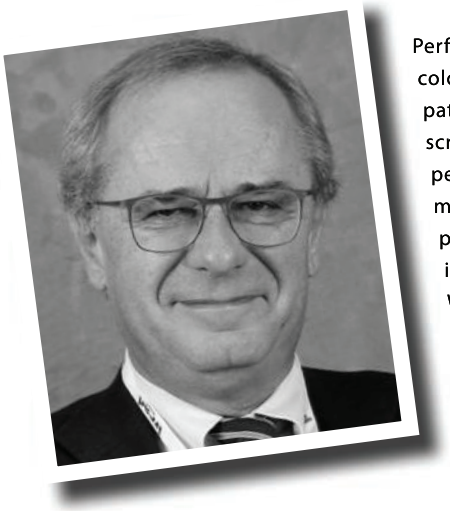
Updates on Screening and Diagnostic Colonoscopy for Colorectal Cancer

Colorectal cancer (CRC) is the most common GI cancer in Europe, with estimates of more than 300,000 new cases reported annually in the EU.[1] Screening for CRC can save lives.

Two late-breaking abstracts at UEG Week 2015 discussed practical ways of refining screening to meet the needs of both patients and healthcare systems.

A national CRC screening programme using biennial faecal immunohistochemical testing (FIT) was launched in the Netherlands in 2014. Using data from almost 530,000 people in this programme, researchers showed how real-time monitoring could be used to make instant adjustments to improve the programme's performance (Abstract LB5727). Raising FIT cut-off from 15 to 47 µg Hb/g faeces, to accommodate colonoscopy capacity and balance the benefits and risks of screening, led to a 28% reduction in the age-adjusted positivity rate (from 9.6% to 6.9%). However, detection rates for CRC and advanced adenoma were maintained at 82% and 75% of the levels reported at the lower FIT cut-off.

CRC screening results categorise patients into risk groups. A Spanish study of 561 patients undergoing index and follow-up colonoscopy determined that intermediate-risk patients with 3–4 small adenomas (<10 mm) could actually be re-categorised as low risk (Abstract LB5575). The advanced lesion detection rate among patients with 3–4 small adenomas only was significantly lower than that for patients with 3–4 adenomas plus at least one measuring ≥10–<20 mm (4.8% versus 16.7%, p<0.001). There was no significant association between the presence of 3–4 small adenomas only and advanced colorectal neoplasia (p=0.065).



"High quality colonoscopy is an increasingly important diagnostic and therapeutic tool and it is important that we constantly striveto improve our capabilities"

Perforations are a risk during colonoscopy — performed on patients with abnormal CRC screening results. A survey of perforations occurring during more than 260,000 endoscopic procedures in the UK revealed in a presentation at UEG Week 2015 that diagnostic perforations occurred most commonly in the sigmoid colon and were significantly associated with the need for surgery (p=0.001), post-perforation morbidity (p=0.009) and stoma formation when compared with all other colorectal locations (Abstract OP001).

Comments

Commenting on the results of this survey, Professor Guido Costamagna (left) from Università Cattolica del Sacro Cuorein Rome, Italy and 'UEG Week News' Editor-in-Chief said: "High quality colonoscopy is an increasingly important diagnostic and therapeutic tool and itis important that we constantly striveto improve our capabilities. These study findings provide valuable information for endoscopists and should facilitate improvements in the managementof patients undergoing colonoscopy."

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Obesity & Excessive Weight Gain During Pregnancy - Childhood Obesity Risks

Overweight and obese women who gain excessive weight during pregnancy may be putting their babies at risk of a lifetime of obesity.

Experts from United European Gastroenterology are calling for women of childbearing age to aim to maintain a normal body weight, and for expectant mothers to stay physically active and consume a balanced diet to avoid permanent damage to their child's health.

Speaking at the 23rd United European Gastroenterology Week (UEG Week 2015) in Barcelona, Spain, Professor Berthold Koletzko (right) from Hauner Children's Hospital at the University of Munich, Germany, explains that evidence is mounting that excessive weight gain as well as early nutrition play a vital role in many aspects of future health. "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"[1].

Childhood Obesity Epidemic

The incidence of obesity among children is rising at an alarming rate. According to the World Health Organisation, between 1990 and 2013, the number of obese children aged less than 6 years increased from 32 million to 44 million globally – an increase of almost 40%.[2] If current trends continue, by 2025, it has been estimated there will be 70 million obese young children worldwide.[2]

> "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"

Many factors contribute to the development of obesity in childhood, including the child's genetic make-up, the consumption of energy-dense, high-fat, high-sugar and high-salt foods, and a lack of physical activity.[3] Studies have also suggested that overweight and obese women at the time when they become pregnant are much more likely to have fatter children than those who are not overweight before or during pregnancy.[4] According to Prof. Koletzko, exposure of the unborn child to an excess of fuels such as glucose and fatty acids may cause permanent metabolic reprogramming in the child that leads to life-long obesity after birth.

"Perhaps even more worryingly, these metabolic and epigenetic changes can be passed from generation to generation, which has major public health implications," he said.

Lifestyle During Pregnancy and Optimised Infant Feeding

Maintaining physical activity and following a balanced diet with limited sugar and saturated fat during pregnancy can be effective in reducing a very high birth weight of babies,[5] a key risk factor for obesity in later life.[6] After birth, improved infant feeding is an effective tool for obesity prevention. In a large controlled study including children in five European countries, Prof. Koletzko and his team demonstrated that an improved infant formula, with lowered protein content - more similar to the protein level in breast milk – lowered

the rate of obesity at the early age of 2 by 9 fold, as compared to conventional protein-rich bottle milk. He comments "These results demonstrate that improving nutrition and lifestyle during the first 1,000 days of life, including pregnancy and the first two years of childhood, provide enormous opportunity for improving lifelong health and well-being".

The Early Nutrition Project

Prof. Koletzko and researchers from 12 European countries, the USA and Australia have launched the Early Nutrition Project (http://www.project-earlynutrition.eu/eneu/) to study how early nutritional programming and lifestyle factors impact the rates of obesity and related disorders, with a budget of more than 11 million Euros. "We believe that if we can understand how metabolic reprogramming in early life alters an individual's susceptibility to becoming overweight, we might be able to intervene to prevent or even reverse the process," he said.

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Endoscopic Resection in the Lower GI Tract: Latest Data and Discussions

Late-breaking abstract presentations at UEG Week 2015 discussed results from studies of endoscopic resection in the colon, with practical implications.

Dr Arthur Schmidt from Klinikum Ludwigsburg, Germany, presented preliminary results of a prospective, multicentre trial suggesting that full thickness resection (FTR) is feasible with a novel over-the-scope device (Abstract LB5715).

The device was used to perform procedures on 79 patients with adenomas, T1-carcinomas or subepithelial tumours at various sites along the lower gastrointestinal tract. The target lesion was reached in all cases; the technical success rate was 86.0% and the R0 resection rate was 78.2%. One secondary perforation at the resection site required surgical therapy and two cases of minor bleeding were observed. Final results from the trial are expected by mid-2016.

Dr David Tate from Westmead Hospital, Sydney, Australia, described how the Sydney endoscopic mucosal resection (EMR) recurrence tool (SERT) can be used to determine appropriate first surveillance times following EMR of colonic lesions (Abstract LB5586). The four-point clinical score system to estimate the probability of recurrence was based on an analysis of 1,383 lesions that were eligible for first surveillance colonoscopy at median 5 months. Independent predictors of recurrence were identified as lateral spreading lesion size ≥40 mm (score=2), intra-procedural bleeding (score=1) and high-grade dysplasia (score=1).

SERT 0 lesions had a negative predictive value of 92.6% for recurrence at first surveillance colonoscopy.

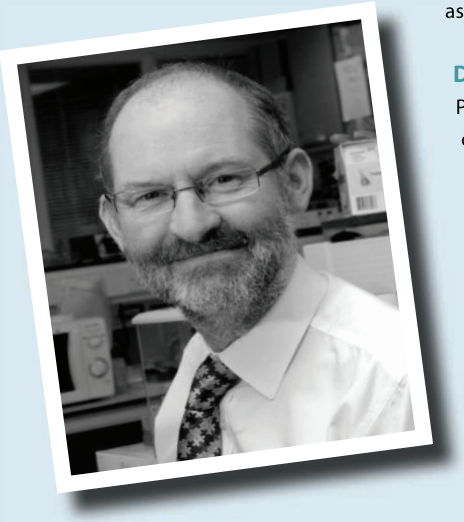
Six-month cumulative recurrence rates were 14.8% for SERT 1–4 lesions but only 5.6% for SERT 0 lesions, climbing to 46.6% and 16.8%, respectively, at 36 months.

"Conducting a first surveillance of SERT 0 lesions at 18 months is safe and will result in substantial cost savings", Dr Tate told UEG delegates.

Increased Risk of Large Bowel Cancer for Each cm Rise in Waist Circumference

Experts speaking at the 23rd United European Gastroenterology Week (UEG Week 2015) in Barcelona, Spain revealed compelling evidence of the link between excess body weight and risk of colorectal cancer (CRC).

John Mathers, (right), Professor of Human Nutrition from the Institute of Cellular Medicine at Newcastle University in the UK presented data showing an overall increase of 18% in relative risk of CRC per 5 unit increase in BMI.[1]



"In addition, in men, there is now evidence that increasing waist circumference in middle age is associated with increased bowel cancer risk," says Prof. Mathers. CRC risk was increased by nearly 60% in men who gained at least 10 cm in waist circumference over 10 years.[2] "This increased cancer risk may be due to persistent inflammation in people with obesity."

Patients with Lynch Syndrome

Patients with Lynch Syndrome (LS) have a higher than normal risk of CRC because of an inherited defect in one of the genes responsible for repairing DNA. Prof. Mathers presented new data showing that, in people with Lynch Syndrome, CRC risk increases with higher body weight and for those who are obese the risk of CRC is doubled.[3] Quite surprisingly, the increase in CRC risk with higher body weight in people with Lynch Syndrome was about twice as great as that seen in the general population.

Dietry Choices and Lifestyle

Prof. Mathers said "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."

In addition, for those people who are already too heavy, losing weight may reduce their CRC risk but this is an area which requires further study. In his studies with Lynch Syndrome patients, Prof. Mathers observed that aspirin lowered the excess CRC risk seen in patients with obesity, perhaps through its anti-inflammatory effects.[3] "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."

Bowel Cancer

"Bowel cancer is strongly associated with age, obesity and diet – and is driven by inflammation," explains Prof. Mathers. "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."

"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" said John Mathers, Professor of Human Nutrition from the Institute of Cellular Medicine at Newcastle University, UK

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Drinking Trends Across Europe Increasing Bowel Cancer Risk

It has been estimated that around one in 10 cases of bowel cancer can be linked to alcohol consumption and the risk increases the more alcohol you drink.

One international group of researchers has estimated that the bowel cancer risk increases by 21% if you have two or three alcoholic drinks a day (1.5 to 6 units of alcohol) and by more than 50% if you have four or more drinks a day (6 units or more). Even having one alcoholic drink a day (1 unit) increases the risk by 7%.

Alcohol and Bowel Cancer

Many people understand that alcohol damages the liver, but the strong link between alcohol and bowel cancer is less well known. Now, experts are calling for a more concerted effort to conduct further research and raise awareness of the link between alcohol and bowel cancer in order to reduce the incidence of one of Europe's most common cancers.

"Alcohol is one of the most serious and avoidable risk factors for bowel cancer and we need to take urgent steps and use different approaches to raising awareness of this issue and to encouraging people to reduce their alcohol intake," explains Professor Patrizia Burra, (right), from United European Gastroenterology (UEG).

"Of major concern is that younger people are now drinking more heavily and often in dangerous or hazardous ways and we expect this to have a significant impact on future bowel cancer incidence rates."

The association between alcohol intake and bowel cancer appears to be stronger in men, with one fourth of bowel cancer cases in men attributable to an alcohol intake of more than 23 g/day. The link is also stronger amongst Asian populations and in those who combine drinking alcohol with either smoking, being over-weight or high red meat intake.

"Of major concern is that younger people are now drinking more heavily and often in dangerous or hazardous ways and we expect this to have a significant impact on future bowel cancer incidence rates"

Alcohol Consumption

Alcohol consumption is a major public health concern and Europe has the highest levels of drinkers in the world. The EU currently has the highest alcohol consumption, on average consuming 12.51 litres of pure alcohol per person, more than double the worldwide average.

European Code

"We now have a European Code Against Cancer that highlights 12 ways that individuals can reduce their cancer risk," says Prof. Burra. "This emphasizes that not drinking alcohol is better for cancer prevention which is a great start, but successful cancer prevention requires a combination of individual action and support for individuals to make the lifestyle changes needed to stay healthy. If we don't change our approach to alcohol consumption now, we face serious health and economic repercussions for future generations. We must make people think twice about drinking any amount of alcohol but being realistic, the basic message has to be that less is better."

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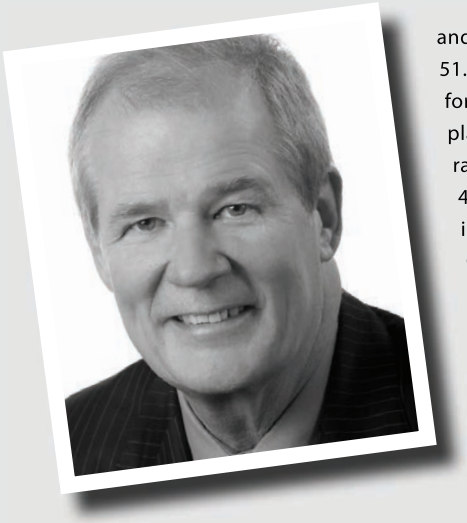
Novel Immunotherapy for TNF-α-naïve Crohn's Disease

The novel anti-interleukin-12 (IL-12)/23p40 antibody, ustekinumab, significantly improves clinical outcome in patients with Crohn's disease not refractory to anti-tumour necrosis factor (TNF)-α treatment. This was the finding of a randomised phase III study reported by Dr Brian Feagan, (right), from Robarts Clinical Trials, University of Western Ontario, Canada, in a late-breaking abstract presentation (Abstract LB5668).



The positive effects of ustekinumab in patients failing on anti-TNF-α agents have previously been confirmed[1] and this study looked for the first time at patients with moderate-to-severe active disease failing conventional therapy.

Over two-thirds (69%) of the 628 patients were anti-TNF treatment-naïve. At Week 6, the clinical response rates for placebo, ustekinumab 130 mg and ustekinumab 6 mg/kg, were 28.7%, 51.7% and 55.5%, respectively ($p<0.001$ for both doses of ustekinumab versus placebo). Corresponding clinical remission rates at Week 8 were 19.6%, 30.6% and 40.2%. Significant ustekinumab-related improvements were also noted in the Crohn's Disease Activity Index and the Inflammatory Bowel Disease Questionnaire

The incidence of adverse events, including serious infections, was similar between the ustekinumab and placebo groups.

> "Our study confirms that ustekinumab provides effective disease control and improves the quality of life of patients failing all types of previous therapy, not just anti-TNF treatment"

"Our study confirms that ustekinumab provides effective disease control and improves the quality of life of patients failing all types of previous therapy, not just anti-TNF treatment," observed Dr Feagan.

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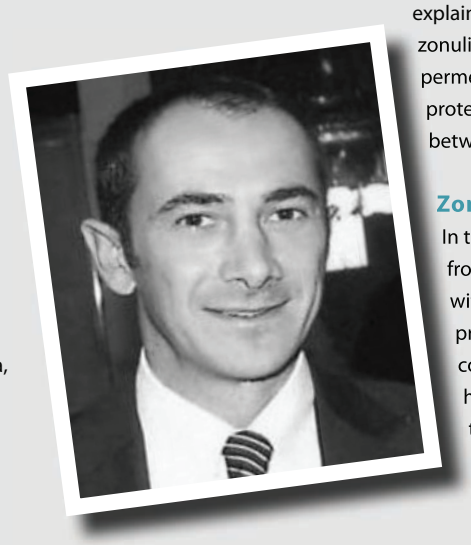
Zonulin in the Spotlight as Researchers Find New Link with Non-coeliac Gluten Sensitivity and IBS

The intriguing story of the recently-discovered protein, zonulin, advances a chapter as Italian scientists announce the results of their latest research linking zonulin with two common inflammatory bowel conditions.[1]

The researchers have discovered that people with non-coeliac gluten sensitivity (NCGS) and irritable bowel syndrome (IBS) have higher than normal blood levels of zonulin, suggesting an important role for the protein in the development of these conditions. Speaking at the 23rd United European Gastroenterology Week (UEG Week 2015) in Barcelona, Spain, Professor Giovanni Barbara, (right), from the University of Bologna said the results may lead to new treatment strategies for these conditions. "We were intrigued to find that blood levels of zonulin were almost as high in patients with NCGS as in those with coeliac disease," he said.



Zonulin in Autoimmune Disease

Zonulin is a type of protein (a haptoglobin) that was discovered in 2000 by a team of researchers at Maryland School of Medicine in the USA. The protein is found within intestinal cells and it is the only human protein discovered so far that regulates the permeability of the intestine. Zonulin has been called a "tight junction regulator", as it controls the size of the gaps between the intestinal cells and orchestrates the passage of nutrients, water and cells into and out of the gut.

Scientists have found that zonulin is produced and released by triggers including intestinal bacterial infections and gluten, and a link between zonulin and coeliac disease has already been established.[2] In the presence of zonulin, the normally tight junctions between the intestinal cells remain open, creating bowel "leakiness" and initiating an inflammatory cascade that eventually damages the intestinal wall.

"Increased intestinal permeability has been implicated in a range of autoimmune conditions including coeliac disease, type 1 diabetes, rheumatoid arthritis and multiple sclerosis," explained Prof. Barbara. "Since zonulin is a key regulator of intestinal permeability, it is possible that this protein provides a common link between all these conditions."

Zonulin in NCGS and IBS

In the latest study, the team from Bologna recruited patients with NCGS (n=27), diarrhoea-predominant IBS (IBS-D) (n=15), coeliac disease (n=15) and healthy volunteers (n=15) and they measured their blood levels of zonulin.[1] The highest zonulin levels were found in the patients with coeliac disease (mean 0.033 ng/mg), followed by those with NCGS (mean 0.030 ng/mg) and IBS-D (mean 0.012 ng/mg). The mean level in the healthy volunteers was only 0.007 ng/mg. In the patients with NCGS, blood levels of zonulin fell significantly when they were eating a gluten-free diet.

> "Hopefully, our work will lead to new diagnostic and therapeutic strategies for patients with these and possibly other 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," said Prof. Barbara. "Hopefully, our work will lead to new diagnostic and therapeutic strategies for patients with these and possibly other autoimmune conditions."

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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).

A recent randomised controlled trial (RCT) tested the efficacy and safety profile of obeticholic acid COCA). 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 f it 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.

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, 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 Lohr, Professor of Gastroenterology and Hepatology, Karolinska Institutet, Stockholm, Sweden.

According to UEG, the responsibility of instigating change with regard to established risk factors for pancreatic cancer 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.

"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 Lohr concluded.

Carcinogenic Risks of Red & Processed Meats

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.

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.

IBS 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 Creactive 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 noninvasive 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.

UEG Launch #FaceUp2CRC Campaign to Raise Awareness of Colorectal Cancer

Colorectal cancer (CRC) is the most common type of gastrointestinal cancer in Europe, with estimates of more than 300,000 new cases recorded in the EU every year. It accounts for approximately half of all GI malignancies in Europe, and the annual incidence is predicted to rise 12% by 2020.

Although most cases of CRC are diagnosed in the over 50's, recent findings have also suggested that the risk of young people developing CRC is increasing at an alarming rate, highlighting the need for greater CRC awareness across all age groups. With early detection resulting in a 90-95% survival rate, United European Gastroenterology (UEG) has launched the '#FaceUp2CRC' campaign and is calling for medical professionals to unite and create a movement to help raise awareness of CRC, encouraging members of the public to undertake screening.

UEG is calling for medical professionals to share their 'selfie' and post this online with the hashtag #FaceUp2CRC. Supporters are invited to be as creative as they like and are encouraged to 'face up' to their camera whilst posting their message.

UEG President Professor Michael Farthing explains "colorectal cancer is treatable when detected early, yet it claims the lives of hundreds of people across Europe every day. We hope that the GI community will come together to help us with this campaign to help raise awareness of CRC and improve screening uptake and survival rates across Europe".

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Current rates for CRC screening programmes vary from as little as 15% in areas of Poland and just 22% in Belgium to a healthier rate of 64% in Norway and 70% in Finland.

However, uptake generally throughout Europe remains alarmingly low, with the percentage of eligible adults screened in many countries falling considerably short of the 65% rate considered desirable by the European commission.

UEG will be promoting the campaign on Twitter, Thunderclap and throughout UEG Week Barcelona 2015.

To find out more about UEG Week, please visit:

www.ueg.eu/week/#FaceUp2CRC

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.

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."

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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 retrospect ive 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 t his analysis it has been suggested t hat care should be taken when prescribing these novel drugs to older patients.

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 met hods 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.

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.

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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UEG Week 2016...

The 23rd UEG Week takes place in Vienna between 15th to 19th October 2016. *Treatment Strategies* takes a look at a number of the finest hotels Vienna has to offer...

HILTON VIENNA
Location - AM STADTPARK 1, A - 1030 VIENNA, AUSTRIA

Set in the centre of Vienna, just 16 minutes from Vienna International Airport via the direct city airport train, the Hilton Vienna hotel is the perfect base to experience everything that the Austrian capital has to offer and is ideal for the congress.

Take in the park or city views from a stylish Guest room at the Hilton Vienna hotel. Get to work at the large desk, surf the web with wireless internet or re-energise in the comfortable armchair.

Executive Rooms and suites enjoy Executive Lounge access complete with complimentary continental breakfast, snacks and drinks. The Hilton Vienna hotel offers a wide range of conference services, from fully equipped Hilton Meetings rooms, benefiting from natural daylight, to the multifunctional Park Congress Centre, with an area of 8880 sq. ft. and capacity for up to 840 delegates.

Whatever the occasion, the Hilton Vienna hotel offers the facilities and services to meet all your business requirements.

Try modern Austrian and European à la carte specials in S'PARKS restaurant, or dine al fresco on the terrace in summer. Enjoy a fine glass of Austrian wine or a sophisticated cocktail and classic bar snacks at the Lobby Bar & Lounge. Maintain your fitness in the well-equipped gym, then take some time out in the sauna, steam bath or the relaxation area at the Hilton Vienna hotel.

HILTON VIENNA PLAZA
Location - ACHOTTENRING 11, A - 1010 VIENNA, AUSTRIA

Conveniently located in the commercial heart of Vienna and close to the historic city centre, the Hilton Vienna Plaza hotel is an ideal base for seeing the Austrian capital's best sights. Just 20 minutes from the airport, the hotel is in the heart of Vienna and less than one kilometer from fantastic sights such as the Hofburg Imperial Palace.

The timelessly designed guest rooms offer a range of thoughtful amenities. Catch up on work at the desk and reinvigorate in the marble bathroom.

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Doing business is easy with ten flexible meeting rooms for 2-150 guests and WiFi throughout the hotel. All meeting rooms offer natural daylight, and A/V equipment rental and videoconferencing are available.

Start the day with a delicious Hilton buffet breakfast at the Brasserie & Bar ÉMILE. This venue takes group bookings for lunch and dinner, and opens for special occasions.

Relax after a busy day at the congress in the sauna or take time out in the relaxing area. Re-energise with a revitalising workout in the fitness center.

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Book early to avoid disapointment. Follow the booking guidelines on the website below.

HILTON VIENNA DANUBE WATERFRONT
Location - HANDELSKAI 269, 1020 VIENNA, AUSTRIA

Explore historic Vienna from the modern riverfront Hilton Vienna Danube Waterfront hotel. With excellent links to the city's public transport network, you are in easy reach of Vienna's major attractions and bustling business districts.

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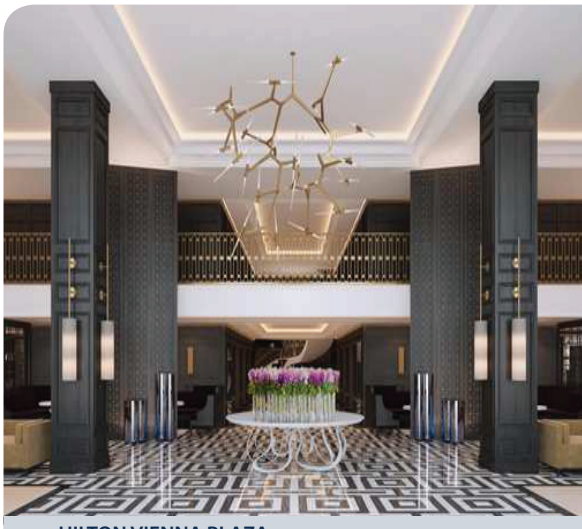
Swim in the outdoor pool while you gaze across the waters of the Danube or stretch out on a sun lounger. Unwind with a workout in the hotel's fitness room or take it easy and soak in the whirlpool. Sit on the riverfront terrace of the "Waterfront Kitchen" or in the bright and trendy dining room and savour locally sourced cuisine with seasonal ingredients from the Alps/Adriatic region in this new Vienna restaurant. Round off busy days with a glass of regional wine, Austrian beer or an expertly prepared cocktail at the Pier 269 Bar & Lounge.

For more information please visit **www3.hilton.com**



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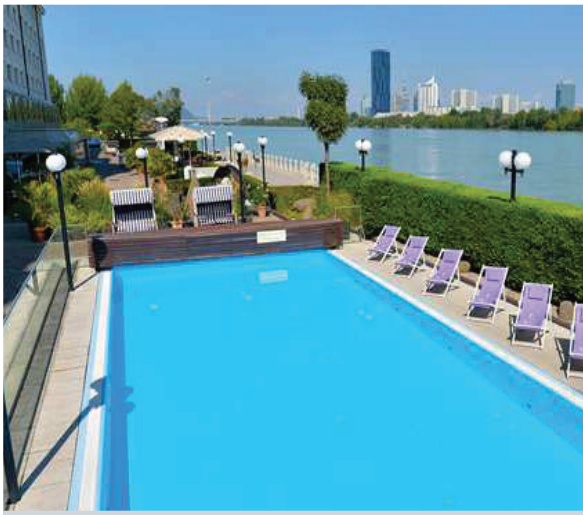

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UEG Week 2016

15th - 19th October 2016

Vienna, Austria

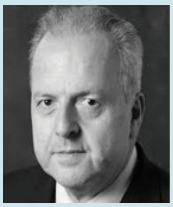
Waking Up to Advanced Chronic Liver Disease: Bright Ideas on Optimising HE Management

Summary of Presentations from the Norgine-supported Satellite Symposium at the United European Gastroenterology Week 2015, Barcelona, Spain, 26th- 28th October 2015

Debbie Shawcross,[1] Paolo Angeli[2] and **Wim Laleman[3]**

1. Senior Lecturer and Honorary Consultant in Hepatology, Institute of Liver Studies and Transplantation, King's College London School of Medicine at King's College Hospital, London, UK; 2. Professor of Internal Medicine and Chief of the Hepatic Emergencies Unit, University of Padova, Padova, Italy; 3. Associate Professor, Department of Gastroenterology, Section Liver and Biliopancreatic Disorders, University Hospitals Leuven, Leuven, Belgium

Dr Debbie Shawcross is a Clinician Scientist based at the Institute of Liver Studies, King's College Hospital, London, UK. She held a HEFCE Clinical Senior Fellowship between January 2008 and 2013 and works as a Consultant Hepatologist on the King's Liver Unit with a specialist interest in hepatic encephalopathy. She is the lead for Education and Training in Hepatology within King's Health Partners, the Academic Health Sciences Centre and is the Training Programme Director for Gastroenterology and Hepatology Specialist Training in South Thames. The aims of her ongoing research programme are to characterise the molecular mechanisms underlying the predisposition to infection in liver failure focusing specifically on neutrophil dysfunction, inflammation and hepatic encephalopathy.



Prof. Paolo Angeli is a Professor of Internal Medicine at the University of Padova, Italy. He is also Head of the Unit of Hepatic Emergencies and Liver Transplantation, a research group working on the pathophysiology and treatment of acute, chronic and acute-on-chronic liver diseases, and on liver transplantation. He is the present Secretary of the International Club of Ascites. Prof. Angeli has previously contributed to guidelines and/or positional papers on the management of ascites, bacterial infections and acute kidney injury in patients with cirrhosis for the European Association for the Study of the Liver. He also contributed to the new diagnostic criteria for acute kidney injury in patients with cirrhosis, which resulted from a consensus process involving almost all the international experts in this field.

Prof. Wim Laleman is Associate Professor in Medicine at the Katholieke Universiteit (KU) Leuven, Belgium. His current research interests include chronic liver diseases and complications (variceal bleeding, hepatorenal syndrome, encephalopathy), acute-on-chronic liver failure, acute liver failure, viral hepatitis, liver transplantation, non-biological extracorporeal liver assist-devices and biliopancreatic disorders and their specific endoscopic (ERCP and EUS) management. He has held the position of Secretary Belgian Association for the Study of the Liver and is currently president of the association. Prof. Laleman is also a member of the European Association for the Study of the Liver (EASL), Belgian Association for the Study of the Liver (BASL), Flemish Society of Gastroenterology (VVGE), Belgian Society of Gastrointestinal Endoscopy (BSGIE) and the European Society of Gastrointestinal Endoscopy (ESGIE).

Introduction

This article discusses the common complications of advanced liver disease and will highlight how hepatic encephalopathy (HE) has a substantial impact on patients and their caregivers or family, and can result in poor outcomes, including increased hospitalisations and death. A co-ordinated approach to the care of patients with chronic advanced liver disease has been shown to improve measures of quality care and this article will provide practical recommendations for managing patients with HE.

Complications of Advanced Chronic Liver Disease: Room for Improvement?

Dr Debbie Shawcross

World-wide, the incidence of cirrhosis is increasing exponentially and it is estimated approximately 5.5 million people are living with cirrhosis in the United States.[1] Data on the prevalence of liver disease in Europe suggest 500,000 Europeans are living with advanced cirrhosis.[2] Chronic liver disease affects most organs of the body (Figure 1) and causes significant morbidity and mortality, mainly due to complications including HE, ascites, hepatorenal syndrome and oesophageal or gastric variceal haemorrhage. It is also associated with a high rate of hospitalisation and readmission, often precipitated by infection. In the US, hospital discharges have been increasing by almost 10% each year.[3]

The natural history of cirrhosis is characterised by a 'compensated' phase (asymptomatic) followed by a 'decompensated' phase marked

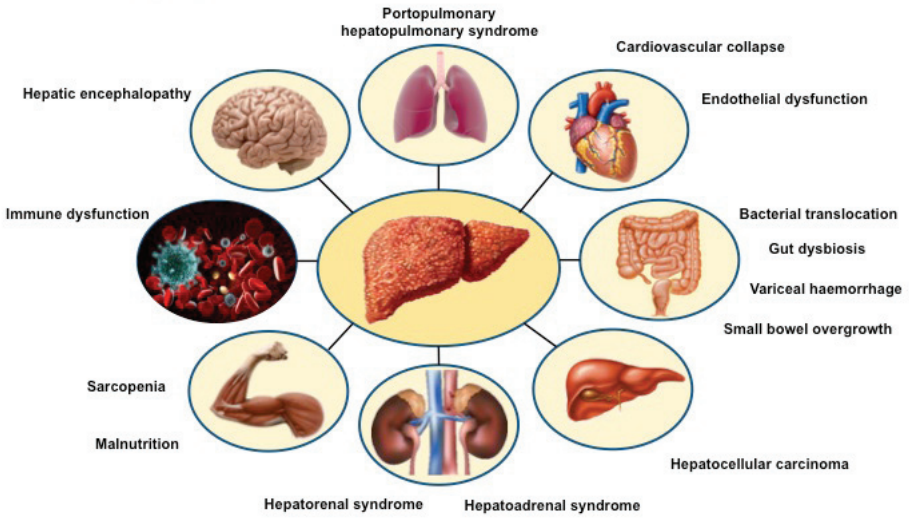


Figure 1. Complications of advanced cirrhosis. Figure courtesy of Dr Debbie Shawcross.

by the development of complications of portal hypertension and/or liver dysfunction. This can be rapidly progressive and is an important step in prognosis. The 1-year mortality rate for a patient with stage 2 compensated cirrhosis (varices, no ascites) is 3.4% compared to 57% in patients with stage 4, decompensated cirrhosis (bleeding with or without ascites).[4]

HE is a common complication of cirrhosis and US data indicate yearly increases in overt HE-associated discharges.[3] It is probable this is also occurring in most European countries, however these are currently difficult data to track. Approximately 70% of patients with cirrhosis will present with minimal HE, with 23-40% progressing to develop overt HE.[5-8] When a patient develops an overt episode of HE the prognosis is generally poor, with a survival rate of 42% at 1 year and only 28% to 38% at 3 years.[5,9]

The objective of managing HE is to improve the patient's symptoms and to prevent a patient from being readmitted for HE. If this can be achieved there is the potential to substantially reduce healthcare resource use. A retrospective study of 402 patients with cirrhosis hospitalised at an academic transplant centre for ascites, spontaneous bacterial peritonitis, renal failure, hepatic encephalopathy or variceal haemorrhage found that 14% were readmitted within 1 week, and 37% within 1 month.[10]

For most of the complications of cirrhosis management guidelines have been published (and revised) by professional societies.[11] As an example, standardised guidelines for variceal bleeding include screening oesophagogastroduodenoscopy when a diagnosis of cirrhosis is made and reflect recent advances in management including improved endoscopic techniques, use of variceal band ligation, availability of vasopressin analogues and utilisation of early rescue transjugular intrahepatic portosystemic stent shunt (TIPSS). As a result, there has been a 60% reduction in mortality due to variceal bleeding over the last 40 years.[12]

In contrast, advances in the diagnosis and treatment of HE have been slow. In 1966, lactulose was introduced for the treatment of HE,[13] however in many countries it was nearly 45 years before the next advance in management occurred with the approval of rifaximin-α for this indication (2010 by the FDA and 2012 by the EMA).[13] Practice guidelines for the management of HE were not available from either the European Association for the Study of the Liver (EASL) or the American Association for the Study of Liver Diseases (AASLD) until the joint publication in 2014.[11] However, these guidelines reflect the ongoing uncertainties in the field and HE represents a challenge to the practising clinician.

The complications of chronic advanced liver disease, including HE, represent a debilitating condition. Moreover, as the incidence of cirrhosis is increasing, the burden of these complications in terms of patient outcomes and resource use (e.g. hospital admissions) will also increase. While the management of complications such as variceal bleeding has improved, there remains room for improvement in the management of HE.

Co-ordinated Care: An Opportunity to Improve Patient Experience and Outcomes

Prof. Paolo Angeli

The complications of cirrhosis represent a significant burden in terms of resource utilisation, particularly hospitalisation and therefore, on associated costs. The annual rate of hospitalisation for complications of cirrhosis in the US is 23.6/100,000 people, at an estimated average charge of $27,979.[15] Reported costs in Italy are lower, at $12,647 per patient, but this excludes the costs associated with liver transplantation.[16]

The ideal model of specialist care would be capable of:

- Increasing survival rate
- Reducing hospital readmission rate
- Improving quality of life
- Improving the patient's perception of quality of care

To achieve this, it is necessary to consider patients' access to care, adherence to guideline recommendations and the ability to meet all the clinical needs of the patient.

As demonstrated by Kanwal *et al.* (2014), age and race can impact on the quality of care a patient receives.[17] Clinical factors such as MELD score, comorbidities and the healthcare system can also affect the quality of care in patients with decompensated cirrhosis.[18] In general, the effectiveness of intervention by the specialist physician in managing ambulatory patients with chronic diseases is not as firmly established as that of patients hospitalised for acute illnesses.[19] However, if a patient is followed up by a specialist physician, particularly one affiliated with an academic centre, a higher quality of care is observed. Adherence to guideline recommendations also represents a step towards achieving a higher quality of care. In addition, adherence to a hepatocellular carcinoma programme was higher when patients were followed-up by specialists vs. subspecialists.[20]

Indicators of quality of care received by intervention and usual care groups were examined by Wigg *et al.* (2013) in patients with cirrhosis and complications from chronic liver failure.[21] In the intervention group changes were made to the delivery system design (including multidisciplinary team management of patients, nurse home visits, rapid access to care using mobile phone service), decision support, self-management support for patients and clinical information systems (including automated reminders). Attendance at outpatient centres and quality of care was significantly better in the intervention group, although no effect on the number of hospital admissions or quality of life could be identified. Possible reasons for this include the small sample size and the short follow-up period being insufficient to document changes in outcomes.

The management of out-patients with cirrhosis is often entrusted to the primary physician or gastroenterologist, with the support of a specialist in liver diseases who may assess an individual patient "on demand" and/or without the availability of data from laboratory examinations and instrumental procedures in real time.

At the University of Padua a new model was developed – the Care Management Programme (CMP). This is co-ordinated by a consultant hepatologist supported by an integrated team comprising nurses, physicians-in-training and hepatologists. The model is based on laboratory investigations, abdominal ultrasound and upper endoscopy (when needed) in real time and undertaken in collaboration with the patient's general practitioner.

Potential advantages of the CMP include clinical decisions being made in real time, development of educational programmes, optimisation of adherence to guideline recommendations, programming of invasive procedures and real-time information transfer to primary physicians.[16] The benefits of a CMP were demonstrated in a study which found that attending the CMP for more than 2 months increased adherence to a sodium-restricted diet in patients with ascites from around 37% to >50% ($p<0.05$).[22]

In addition, the efficacy and financial sustainability of the CMP as a new model of specialised care was evaluated in a prospective study in patients with cirrhosis or ascites who were admitted over a 6 month period. Patients in the two groups were individually matched for eight variables: age, gender, type of ascites (responsive vs. refractory or recurrent), MELD score, CTP score, aetiology of cirrhosis, local/non-local residence and comorbidities. Forty patients were assigned to the CMP and 60 were assigned to standard outpatient care (SOC). The mean time from inclusion to first visit by a specialist physician was similar between groups (32.2 ± 20.1 days [CMP] vs. 39.0 ± 28.4 days [SOC]; p=NS), however:[16]

- Mean number of 'care management check-ups' in CMP group was lower than mean number of specialist visits in SOC group when adjusted per month of life: 0.28 ± 0.10 (CMP) vs. 0.32 ± 0.43 (SOC); $p<0.001$

- Mean number of 'day hospital' admissions per patient-month of life was higher in CMP group than in SOC group: 0.27 ± 0.38 (CMP) vs. 0.10 ± 0.20 (SOC); $p<0.025$

- Pharmacological prescriptions by specialist physicians were similar between groups (p=NS)

- There was significantly improved 1-year survival in patients who were admitted to the CMP than to SOC (p=0.0086)

A reduction in death due to liver-related causes was also observed ($p<0.05$) with independent predictors for mortality including type of care, refractory or recurrent ascites, renal failure and hyponatraemia.[16] In patients treated under the CMP, the rate of emergency hospital admission at 30 days and also 12 months, and the length of hospital stay were all lower when compared to SOC.[22]

Furthermore, the economic benefits of the CMP were demonstrated. Although the CMP was more expensive than standard care, the costs of emergency hospitalisation (€1,346.80 ± €2,165.28 vs. €2,768.31 ± €3,856.94; p<0.05) and those attributable to global management were significantly reduced (€1,479.19 ± €2,184.43 vs. €2,816.13 ± €3,893.03; p<0.05).[16]

Considerations and Recommendations to Optimise the Management of HE

Prof. Wim Laleman

Hepatic encephalopathy (HE) refers to potentially reversible alterations in autonomy, consciousness, behaviour and psychomotor functions related to an accumulation of toxins due to reduced hepatic detoxification and increased portosystemic shunting.

HE is graded in different degrees of severity and divided in principal into a subclinical covert and clinical overt form, as defined respectively by New Haven grade 1 and grade 2 to 4. Attention needs to be given to further specifying HE with regard to time course (episodic, recurrent or persistent) and whether it is spontaneous or precipitated.

The recently published guidelines from the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) provide a framework for the diagnosis and management of patients with HE.[14] The guidelines state:

1. An episode of overt HE (whether spontaneous or precipitated) should be actively treated
2. Secondary prophylaxis after an episode for overt HE is recommended
3. Primary prophylaxis for prevention of episodes of overt HE is not required, except in patients with cirrhosis with a known high risk to develop HE
4. Recurrent intractable overt HE, together with liver failure, is an indication for liver transplant

Recommendation 1: An Episode of Overt HE Should be Actively Treated

Figure 2 represents the current treatment pathway for an episode of overt HE.[14]

It is important to start by assessing the patient to ensure that they are stabilised with regard to vital signs (the A-B-Cs: airway-breathing-circulation). If the patient has an unsecured airway, they should be intubated and monitored in an Intensive Care or Critical Care Unit. Once vital functions are secured, the second question to be addressed is whether there is an alternate cause for the patient's mental status. These include:

• Metabolic encephalopathy (e.g. hypoxia, ethanol, electrolyte imbalance, ketoacidosis, CO_2 narcosis, carbon monoxide intoxication, medication, Wilson disease, sepsis)

• Intracranial pathology (e.g. bleeding, tumour, epilepsy, encephalitis, meningitis, abscess, cerebrovascular accident)

• Psychiatric causes (e.g. Wernicke-Korsakoff syndrome)

Upon confirming the diagnosis of HE, it is critical to promptly recognise and treat any precipitating factors. Common precipitating factors include hypovolaemia/overuse of diuretics, constipation, infection, upper gastrointestinal bleed, shunts such as a transjugular intrahepatic portosystemic shunt (TIPSS), renal failure and psychoactive medication (i.e. benzodiazepines). In conjunction with treating the precipitating factor, or where no

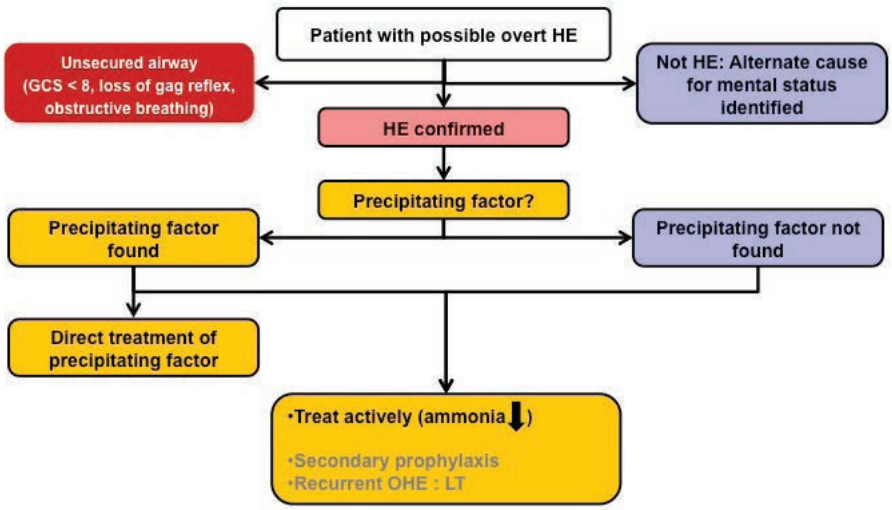


Figure 2. An episode of overt HE should be actively treated.[14]
GCS, Glasgow Coma Scale; LT, lactulose; OHE, overt hepatic encephalopathy.

precipitating factor is present, the objective of treatment is to decrease ammonia levels.

The mainstay of treatment for acute episodes of HE are non-absorbable disaccharides (NADs) such as lactulose and lactitol. Upon entering the gut, NADs are metabolised into volatile fatty acids (VFA) and H+, which lowers the pH of the colon. They are non-digestible in the small intestine, reduce the uptake of glutamine and have the additional cathartic effect of increased levels of gas and osmolality, reducing intraluminal pH and transit time, and bulking of the stool. Although lactulose treatment results in improvement in acute episodes of HE, the effect on mortality is less characterised.[23]

An alternative to lactulose treatment is selective intestinal decontamination by the use of poorly or non-absorbable antibiotics. Metronidazole and vancomycin have previously been used but they are no longer recommended due to adverse events and the development of resistant enterococci. Neomycin is also used and considered safe if used with care.

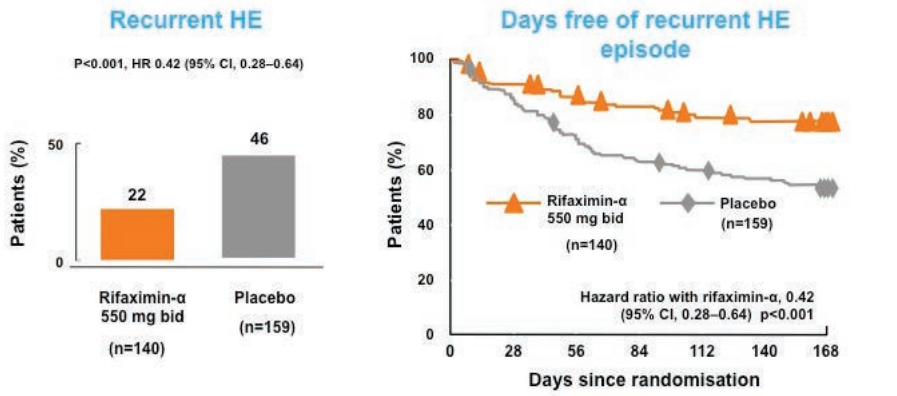
Rifaximin-α is a semisynthetic antibiotic based on rifamycin. The pregnane-X-receptor activator has minimal systemic drug absorption (0.4%), meaning gut concentrations of rifaximin-α remain high. Rifaximin-α is generally well tolerated and dose adjustments are not needed in patients with hepatic dysfunction, including HE. There is also a low likelihood of drug interactions metabolised via cytochrome P450.[24-26] The combination of lactulose plus rifaximin-α was found to be more effective than lactulose alone in the treatment of overt HE although in many countries rifaximin-α is approved only for the prevention of recurrence of HE.[27]

Recommendation 2: Secondary Prophylaxis after an Episode of Overt HE is Recommended

Once a patient has developed overt HE, without prophylaxis they are prone to suffer from further episodes. The recurrence rate within the first year after an over episode of HE is estimated at 40%.[14] The most important non-medical intervention is nutritional support; small, frequent meals, a protein intake of 80-100 g per day and continued physical activity are all recommended.[14]

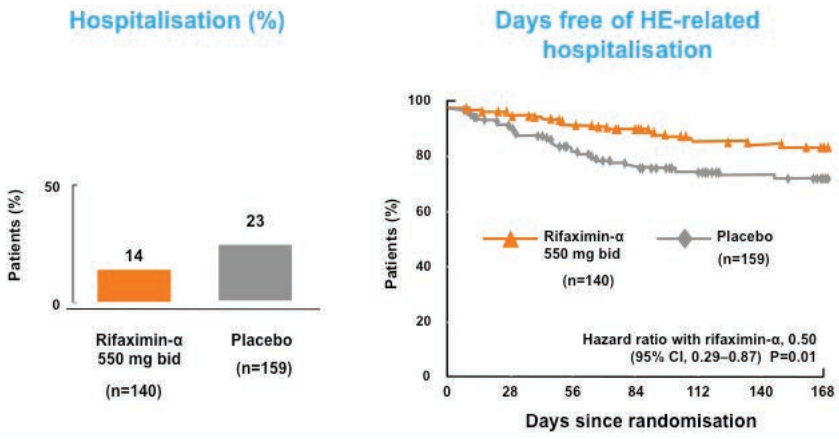
Medically, lactulose is the mainstay for secondary prophylaxis and, when compared to placebo, it significantly reduced breakthrough episodes of HE in patients with cirrhosis who had previously recovered from HE.[28] The dose of lactulose should be carefully titrated so that the patient has two or three loose stools each day without diarrhoea.[14] For patients who are unable to tolerate lactulose, or who suffer from a second bout of HE despite lactulose therapy, rifaximin-α 550 mg twice-daily is recommended.

In a randomised, double-blind, placebo-controlled trial in 299 patients who experienced at least two previous episodes of overt HE, treatment with rifaximin-α 550 mg twice-daily over a 6-month period reduced the risk of a recurrent episode of HE (58% RR, 23.8% absolute risk reduction, NNT [number needed to treat] =4; Figure 3) and significantly



58% risk reduction (NNT = 4 over 6 months)

Figure 3. Time to first breakthrough HE episode.[29]



50% risk reduction (NNT= 9 over 6 months)

Figure 4. Time to first HE-related hospitalisation.[29]

reduced the risk of hospitalisation (50% RR, 9% absolute risk reduction, NNT=9; Figure 4).[29]

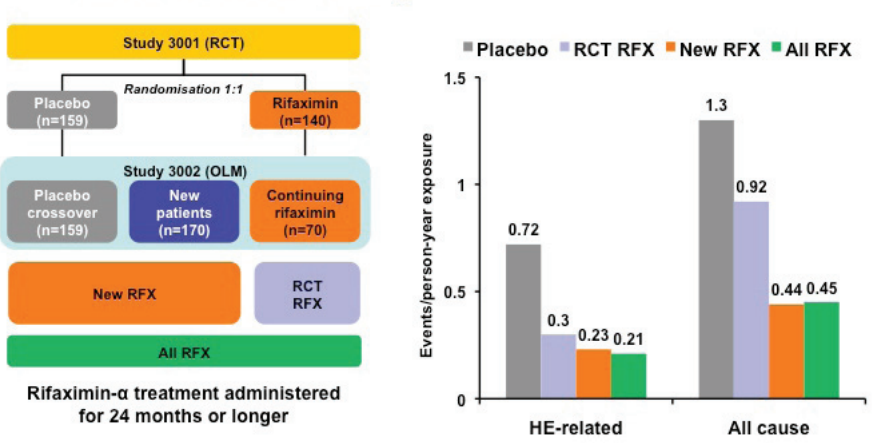
The majority of patients (91%) were recieving ongoing lactulose therapy and the risk of recurrence in the 'placebo' arm (i.e. patients taking lactulose alone despite 'failure') also confirms the need for additional interventions in these patients.

An open-label extension confirmed the repeatability and durability of results from the randomised controlled trial. Patients switching to rifaximin-α from placebo gained a similar therapeutic benefit.[30] In addition, long-term treatment (≥24 months) provided a continued reduction in the rate of HE-related and all-cause hospitalisation, without an increased rate of adverse events (Figure 5).[31]

In addition to lactulose and rifaximin-α there are other treatments available for secondary prophylaxis, including:[14,32,33]

- Ammonia-reducing treatments
  - IV L-Ornithine-L-Aspartate (LOLA)
  - Low-protein diet; NOT RECOMMENDED
- Treatments based on "false neurotransmitter hypothesis"
  - Oral branched-chain amino acids (BCAA)
- Gamma-aminobutyric acid (GABA)-hypothesis treatments
  - Anti-benzodiazepine receptor antagonists (i.e. Flumazenil)
- Probiotics

However, clinical evidence on the use of these treatments is limited to preliminary or minimal data and not all of these are available in all countries.



Long-term treatment rifaximin-α (‡24 months) provides a continued reduction of *HE-related and all-cause hospitalisation*, without an increased rate of adverse events.

Figure 5. Overview of the open label maintenance study.[31]
OLM, open label maintenance; RCT, randomised controlled trial; RFX, rifaximin-α.

Recommendation 3: Primary Prophylaxis for Overt HE is not Required, Except for High-risk Patients

Acute variceal bleed (AVB) represents an important precipitating factor for HE. The role of lactulose for prophylaxis of HE after AVB was examined in 70 patients with cirrhosis. Nineteen (27%) patients developed HE; five patients (14%) in the group that received lactulose treatment and 14 patients (40%) in the placebo group (p=0.03), indicating that lactulose may be effective in the prevention of HE in patients with cirrhosis and AVB.[34] In a more recent study lactulose and rifaximin-α were found to be equally effective for prophylaxis of HE after AVB.[35]

Recommendation 4: Recurrent Intractable Overt HE with Liver Failure is an Indication for Liver Transplantation

Large spontaneous portosystemic shunts (SPSSs) have previously been suggested to sustain HE in refractory HE patients. It has been suggested that 46-70% of patients with refractory HE show large SPSSs upon radiological screening, indicating that the presence of a SPSS not only provides an explanation for the persistence or recurrence of HE despite an acceptable liver function, but may also represent a therapeutic target.[36]

A retrospective analysis assessed the efficacy and safety of refractory HE patients treated with embolisation of large SPSSs for the treatment of chronic therapy-refractory HE. On a short-term basis (i.e. within 100 days after embolisation), 22 of 37 patients (59.4%) were free of HE (p<0.001 vs. before embolisation) of whom 18 (48.6% of patients overall) remained HE-free over a mean follow-up period of 697 ± 157 days (p<0.001 vs. before embolisation). Overall, improved autonomy, decreased number of hospitalisations, and severity of the worst HE episode after embolisation was observed in three-quarters of the patients. With regards to safety, one major non-lethal procedure-related complication was reported. No significant increase in *de novo* development or aggravation of pre-existing varices, portal hypertensive gastropathy, or ascites was reported.[36]

Summary

HE is a severe complication of advanced chronic liver disease, with significant impact on the patient, the healthcare system and on the economy. Overt HE represents a major complication of cirrhosis and is associated with high morbidity

and mortality, and a high risk of recurrence, which therefore warrants appropriate treatment. The implementation of a prompt treatment algorithm is needed and secondary prophylaxis after an episode of overt HE is recommended to prevent further episodes. In order to maximise the benefits from therapy however, an agreed standard of care is required in order to improve patient outcomes, reduce hospital admissions and to improve the economic impact of this debilitating condition. A coordinated approach such as that described in the CMP model may help reduce the complications associated with cirrhosis, aid in the implementation of prompt and sustained treatment and provide the opportunity to improve long-term management.

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An Update on the Treatment of *Helicobacter Pylori* Infection

Sinead Marian Smith

Department of Clinical Medicine, School of Medicine; School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Dublin, Ireland

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 amoxicill in (1,000 mg) taken twice daily for 7-14 days (Tab le 1).[6-8] Metronidazole (500 mg) is used instead of amoxicillin in penicillin-allergic individuals. Unfortunately, the success rate of firstline triple therapy has fa llen 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 fai lure, including high bacterial load, low gastric pH, and impaired mucosal immunity,[11] although the main reasons for *H. pylori* treatment fa ilure 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-analys is 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 res istance.[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]

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

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)

Table 1. *Helicobacter pylori* treatment regimens.
*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.

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 Thai land than northeastern 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 bismuthcontaining 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 proposed as an alternative therapy has been 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 metaanalysis 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

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

Table 2. Recent data on the prevalence of *Helicobacter pylori* antibiotic resistance.
*Primary resistance rate; **Overall resistance rate. Clar: clarithromycin; Met: metronidazole; Lev: levofloxacin; ND: not determined.

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	

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

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 firstline 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 mm1mum 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 sameday 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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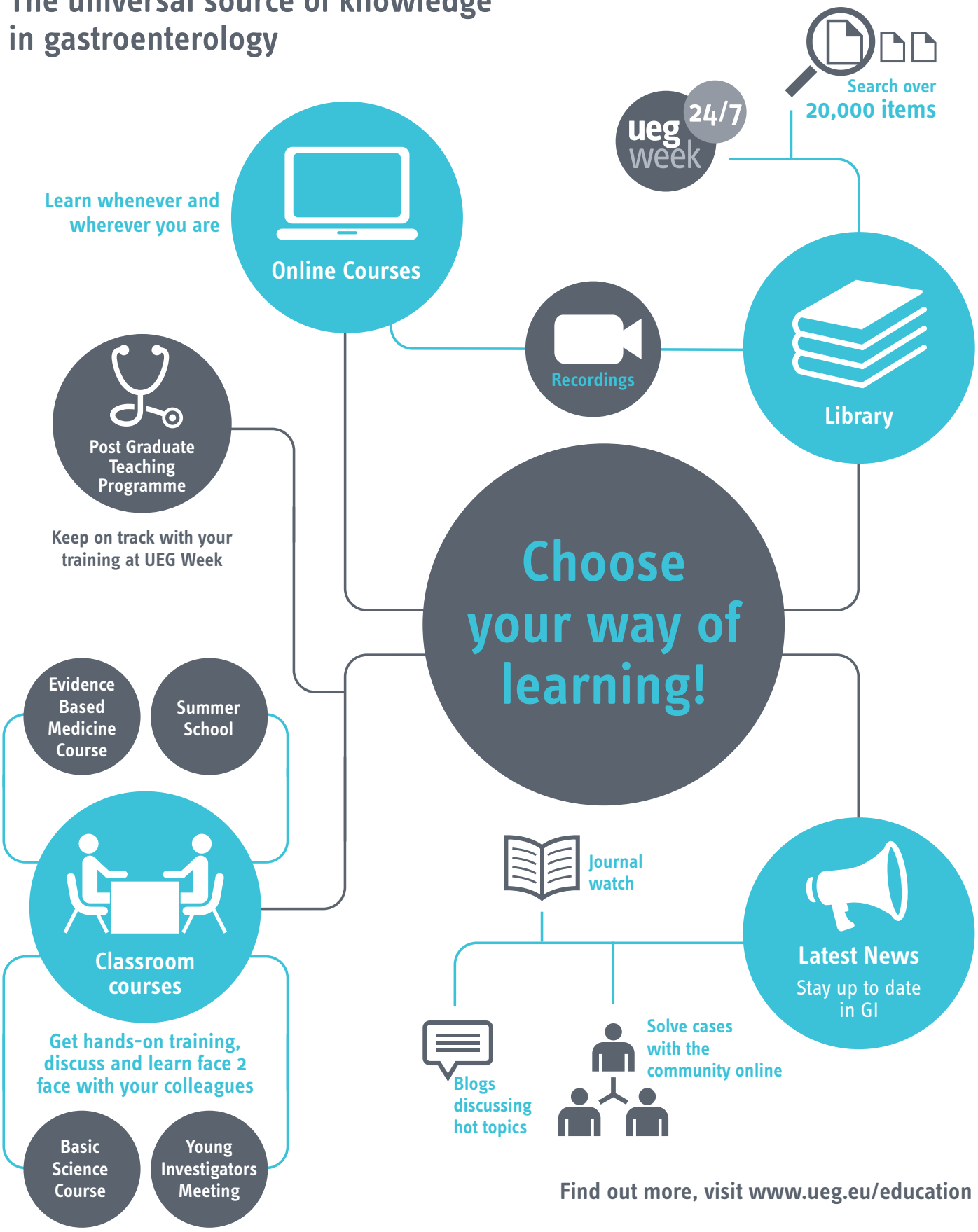

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Management of Diverticulitis and Prevention of Recurrence

Paolo Andreozzi, Francesco Paolo Zito, Giovanni Sarnelli and **Rosario Cuomo**

Department of Clinical Medicine and Surgery, Gastroenterological Unit, University Federico II, Naples, Italy

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, lowgrade 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 (paralyticileus) 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]

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, (-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

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%

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

(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 sconng the severity of diverticulitis is Hinchey's system. Hinchey's classification categorises peritonit is 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 peritonit is. 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 fai lure, malignant haematological diseases, HIV infection, chemotherapy, steroid therapy, or transplantation).[22]

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 noncomplicated acute diverticulitis. However, in recent years several studies have compared antibiotic treatment with no antibiotic treatment in mild

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)

Table 1. Drug regimens commonly used to treat diverticulitis.[21]

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 postdiverticulitis 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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Hepatitis E in Europe: Diagnosis and Treatment

Charlotte M. Nijskens,[1] Suzan D. Pas,[2] Annemiek A. van der Eijk[2] and Robert A. de Man[1]

1. Department of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, Netherlands; 2. Department of Viroscience, Erasmus Medical Center, Rotterdam, Netherlands

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 antiHEV 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 gammaglutamyltranspeptidase.[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 H EV.[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-Barre 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 RTPCR 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 qRTPCR 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 followup 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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UNITED EUROPEAN GASTROENTEROLOGY

ueg education

Young Investigators Meeting

April 22-24, 2016 (Application deadline: January 17, 2016)
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Upcoming Congresses and Meetings

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 Dusseldorf International Endoscopy Symposium

11th - 13th February 2016

Dusseldorf, Germany

The Dusseldorf 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-todate 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® (DOW) 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 The Cambridge Research Centre'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.

www.ueg.org

United European Gastroenterology (UEG) Week 2016

15th - 19th October 2016

Vienna, Austria

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References: 1. Entyvio Summary of Product Characteristics. Takeda Pharma A/S. 2015.
2. Entyvio Prescribing Information. Takeda Pharmaceuticals America, Inc. 2014.

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DATE OF PREPARATION: NOVEMBER 2015

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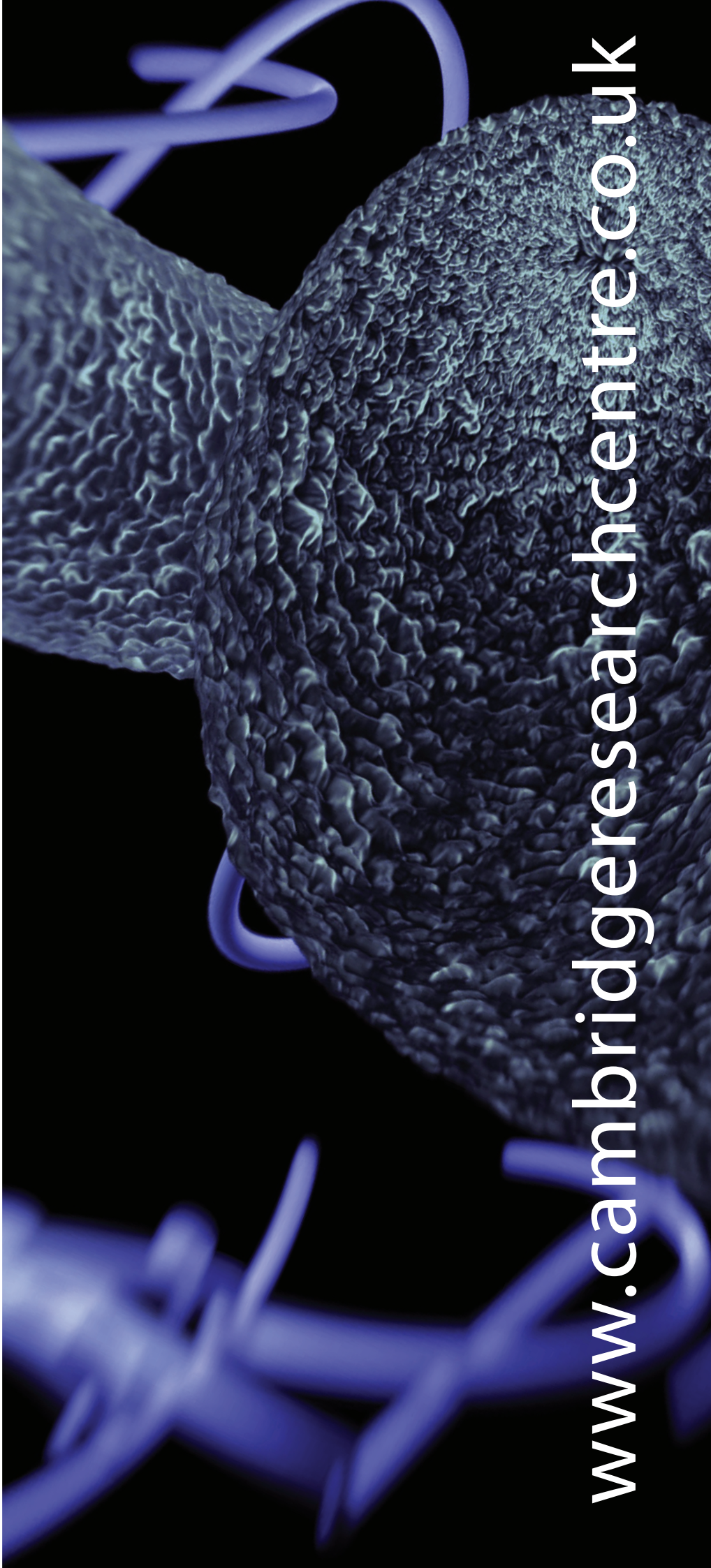
Corticosteroids may be reduced/discontinued in patients who respond to treatment with Entyvio. If therapy is interrupted and needs to be restarted, Entyvio dosing every 4 weeks may be considered. Crohn's disease: Recommended dose regimen is 300mg administered by intravenous infusion over approximately 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.

Adverse events should be reported to the authorities in your country as required by local law. Reporting forms and information can be found at www.takeda.com. Adverse events should also be reported to Takeda at takedasafety@tgrd.com.



The Cambridge Research Centre
Coppergate House
16 Brune Street
London
E1 7NJ