EMJ EUROPEAN MEDICAL JOURNAL

GASTROENTEROLOGY

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INSIDE

Review of

UEG 2014

Vienna, Austria

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GASTROENTEROLOGY

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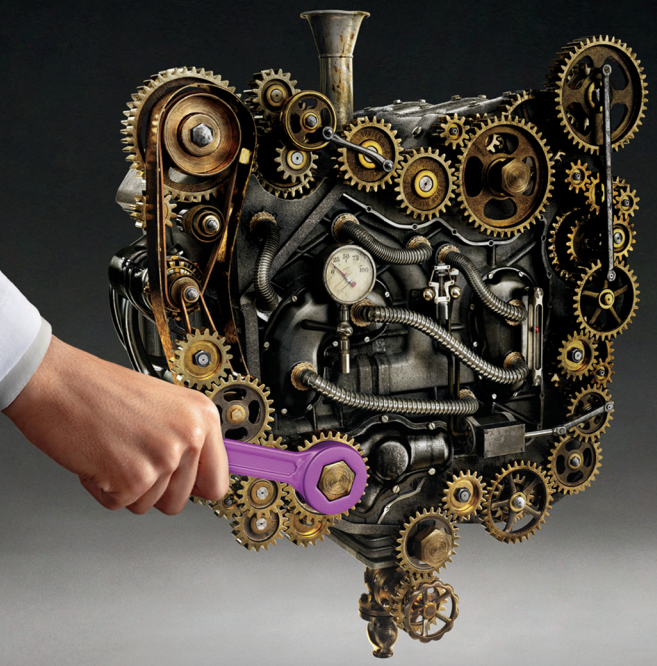
Introducing Entyvio: the first and only gut-selective biologic for patients with ulcerative colitis (UC) or Crohn's disease (CD)[1]

TREAT WITH PRECISION



The first and only gut-selective biologic[1]

- Achieves lasting remission in 42% UC and 39% CD patients at 52 weeks[1]
- Over 3,300 patients monitored on Entyvio[2]
- Targeted mechanism of action[1] different from anti-TNFα therapies
- One dose for all patients[1]: 300-mg IV infusion

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

ITEM CODE: GLO/EYV/2014-00036
DATE OF PREPARATION: NOVEMBER 2014

Entyvio® ▼
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Entyvio® ▼ (vedolizumab) This medicinal product is subject to additional monitoring.
PRESCRIBING INFORMATION
Refer to the Summary of Product Characteristics (SmPC) before prescribing.

Presentation: 300 mg powder for concentrate for solution for infusion. **Indication:** Ulcerative colitis (UC): Adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist. Crohn's Disease (CD): Adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist. **Dosage & Administration:** Treatment should be initiated and supervised by a specialist healthcare professional experienced in the diagnosis and treatment of ulcerative colitis or Crohn's disease. Patients should be monitored during and after infusion. Ulcerative colitis: Recommended dose regimen is 300mg administered by intravenous infusion over 30 minutes at 0, 2 and 6 weeks and then every 8 weeks thereafter. Reconsider treatment if no evidence of therapeutic benefit at week 10. If patients experience a decrease in their response, they may benefit from an increased dosage frequency of 300mg every 4 weeks. Corticosteroids may be reduced/discontinued in patients who respond to treatment with Entyvio. If therapy is interrupted and needs to be restarted, Entyvio dosing every 4 weeks may be considered. Crohn's disease: Recommended dose regimen is 300mg administered by intravenous infusion over 30 minutes at 0, 2 and 6 weeks and then every 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 is available on the safety and efficacy of Entyvio in children aged 0-17 years. Elderly patients: No dosage adjustment required. Renal or hepatic impairment: Entyvio has not been studied in these populations and 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: Entyvio is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding in patients who develop a 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 PML a potential fatal opportunistic infection caused by John Cunningham (JC) virus has occurred in patients treated with other integrin receptor antagonists and systemic immunosuppressive agents. Monitor patients for any new or worsening neurological signs/symptoms. Malignancy: There is an increased risk of malignancy in UC and CD; immunomodulatory products may increase risk. No increased risk with vedolizumab to date. Long term evaluation on-going. 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 normally 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, pruritis, eczema, erythema, night sweats, acne, muscle spasm, back pain, muscular weakness, fatigue, pyrexia. Other serious undesirable effects: respiratory tract infection, infusion site reaction, infusion-related reaction. **Refer to the SmPC for details on full side effect profile and interactions. Marketing Authorisation:** EU/1/14/923/001 300mg powder for concentrate for solution for infusion. Takeda Pharmaceuticals International GmbH is responsible for the sale and supply of Entyvio in Europe. Further information is available from Takeda at www.takeda.com. **PI Approval Code:** EU/1/14/923/001 **Date of revision:** May 2014.

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Welcome

Innovation, best-practice, improving patient outcomes and quality of life, and new endeavours are all areas which this edition of *European Medical Journal Gastroenterology* explores through a range of peer reviewed articles, Congress highlights articles, and news updates.

This journal focuses on a number of topics including: irritable bowel syndrome, upper gastrointestinal (GI) bleeding, small intestinal tumours, Crohn's disease, and colorectal cancer to name but a few. On top of this, we have discussed the progress that has been made in the field and how this impacts clinical practice in our 'Congress Review' section, where you can view the highlights of the 2014 United European Gastroenterology Week Congress.

GI diseases drain European healthcare resources, therefore plans are needed to ensure that patients are always looked after and cared for. The Survey of Digestive Health across Europe, also known as the White Book Report, outlines strategies which hope to guide clinical facilities and research priorities. It is hoped that through these strategies GI healthcare delivery by 2040 will be much more beneficial.

The most common GI emergency is acute upper bleeding; while progress has been made within this area, mortality rates have not significantly improved. To manage this condition a number of recommendations and guidelines have been produced. Taylor et al., in their paper '*The management of acute upper gastrointestinal bleeding; a comparison of current clinical guidelines and best practice*,' have reviewed the National Institute of Clinical Excellence guidelines, the Scottish Intercollegiate Guidelines Network, the American College of Gastroenterology, as well as those published in the Annals of Internal Medicine. Due to a lack of large randomised trials, the guidelines vary; however they do provide a useful framework.

Collaboration amongst the gastroenterology community is greatly encouraged in order for this field to develop, as it is through this partnership that a healthier future for patients can be achieved. One area which is problematic is small bowel tumours; as these have nonspecific symptoms, a prompt diagnosis is not always easy. '*Small intestinal tumours: an overview on classification, diagnosis and treatment*,' written by Dr Notaristefano and Prof Testoni, have discussed new therapies and different treatments which could lead to an improvement in mortality rates. Moreover, they have suggested that understanding aetiopathogenesis can result in an earlier diagnosis and also more effective treatment. Another study, in our 'What's New' section, highlights the benefits of using Botox to suppress tumour growth. This treatment has proved to be an effective anti-cancer therapy with few side-effects.

I would encourage you to read this extraordinary edition of *EMJ Gastroenterology*, and also share it with your colleagues, as it is through education and collaboration that we will reduce the burden of GI diseases.

Spencer Gore

Director, European Medical Journal

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Foreword

Prof Marco Bruno

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

Dear colleagues,

It is my great pleasure to welcome you to the 2014 edition of the *European Medical Journal Gastroenterology*, an open access journal providing high-quality peer reviewed articles covering the wide field of Gastroenterology and also Hepatology. The scientific quality of the journal's content is guarded by an esteemed editorial board composed of well-recognised experts in the field.

For this edition of *EMJ Gastroenterology*, we have assembled a very interesting range of informative original articles, reviews, practice guides, and conference updates. These contributions should not only help you to keep up-to-date with the ever-growing knowledge base in our specialty, but also serve as a challenge for you to consider active participation in the scientific exchange of knowledge and practice experience. For this, we invite you to submit an original article or a review to the journal. A future edition of *EMJ Gastroenterology* may feature your article!

The sessions at this year's United European Gastroenterology (UEG) Week Congress were nothing short of exceptional, and fortunately this journal covers some of the most important updates. Factors which will potentially affect clinical practices in the future were discussed; scientists are urged to discover new approaches to diagnose and treat patients. The Congress also emphasised the need for innovative, technical advances in the non-invasive management of gastrointestinal and hepatic disorders. These events allow professionals to exchange theories and research; together we can establish strategies to foster further progression within this specialised field.

"These contributions should not only help you to keep up-to-date with the ever-growing knowledge base in our speciality, but also serve as a challenge for you to consider active participation in the scientific exchange of knowledge and practice experience."

I would also like to direct your attention to an even easier way of keeping up-to-date by subscribing and joining one of the Journal's social media channels including Facebook, Twitter, and LinkedIn. I hope and trust that reading through this issue of *EMJ Gastroenterology* is rewarding and broadens your knowledge, helping you to provide even better care to your patients.

Kind regards,

Marco J. Bruno

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

UEG WEEK ANNUAL CONGRESS 2014

AUSTRIA CENTER VIENNA, VIENNA, AUSTRIA

18TH-22ND OCTOBER 2014

Welcome to the *European Medical Journal* review of the United European Gastroenterology Week Congress 2014

EMJ EUROPEAN MEDICAL JOURNAL

UEG WEEK ANNUAL CONGRESS 2014

AUSTRIA CENTER VIENNA,
VIENNA, AUSTRIA
18TH-22ND OCTOBER 2014

Welcome to the *European Medical Journal* review of the United European Gastroenterology Week Congress 2014

Spectacular scenery adorned UEG Week 2014, which was held in Vienna, Austria - a cultural and scientific mecca offering the world lashings of visual treats. Drawing 12,500 participants from 118 countries, UEG Week 2014 presented a first-class scientific programme, including >2,000 abstracts and almost 500 lectures, which covered a whole spectrum of gastroenterological and hepatological areas from basic translational science to the latest clinical practice advances. The events also demonstrated great promise for the future of postgraduate education and training.

Attendees from around the world will have seen the development of future international research collaborations. Prof Michael Farthing, UEG President, stressed the importance of face-to-face discussions between clinicians and scientists regarding clinical innovations and research challenges in the face of an increasingly influential online environment; as long as the benefits of real-life interactions are not forgotten, developments in the digital world will surely deliver much for gastroenterological treatments.

"This year we will also have an increasing number of translational basic science sessions, and the topics chosen for these sessions are topics that will probably affect the clinical practice within the foreseeable future. So therefore these sessions should be attractive not only for basic translation scientists but also for clinicians," said Prof Magnus Simren, Chairman of UEG Scientific Committee.

A number of gastroenterological scenarios were outlined which described how the world's position would look by 2040. Prof Farthing expressed the severity of the situation and how, with an

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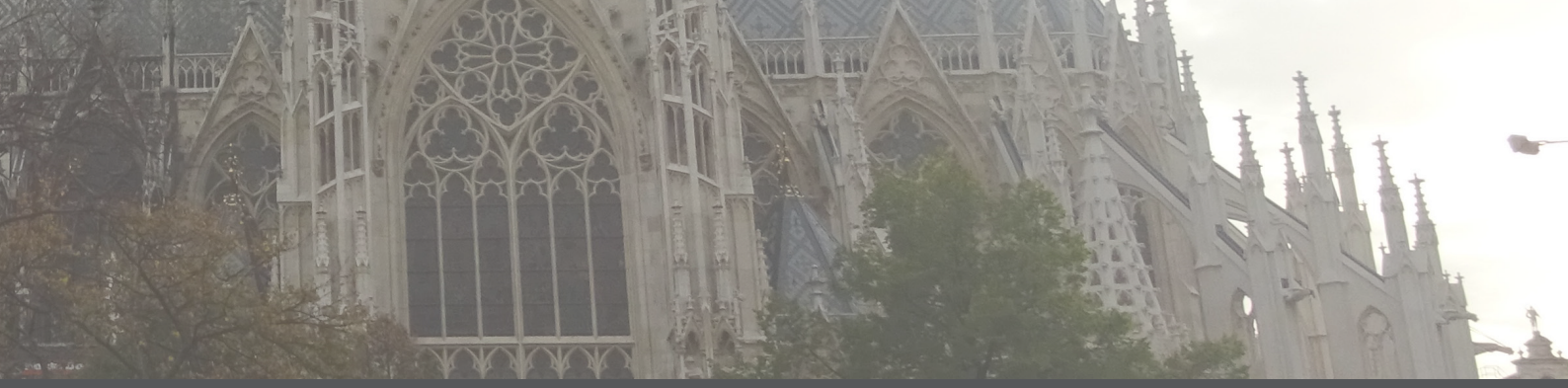
Prof Magnus Simren, Chairman of UEG Scientific Committee



ageing population and declining economy, the current system must change to avoid a veritable doomsday event. The UEG has also outlined what must be done to alleviate the growing crisis of gastrointestinal disorders in Europe in a special report, with knowledge and experience of a far-reaching plethora of problems sadly lacking on much of the continent.

Colorectal cancer (CRC) screening is a wonderful tool for diagnosing and removing CRCs in patients; however, compliance remains unsatisfactory. The emergence of faecal immunochemical testing, which detects the globin segment of haemoglobin in stool sample blood, coupled with strong compatibility allows for highly accurate and personalised screening process.

As with much of medicine in the 21st century, especially treatments for cancer, a personalised approach is leading the way for optimal effectiveness of treatment and compliance; general practitioners are recognised as being well positioned to accomplish individual risk assessments for patients. The debate also rages on as to how *Helicobacter pylori* infection should be managed, with future infection prevention in children posing a major sticking point, while gluten is being increasingly recognised as a major cause of coeliac disease.

The feast of news and developments served up by UEG Week 2014 has given gastroenterologists everywhere a renewed purpose for pursuing progress in their respective fields. Hopes are alive for the reduction of diseases afflicting the digestive system, and as technology advances the revelations at UEG week 2015 are sure to be even more encouraging.

Three-pronged future for European GI healthcare

FUTURE healthcare delivery in Europe lies in the hands of three plausible models, launched by the UEG, to inspire healthcare professionals and policymakers to begin planning for a more sustainable future for digestive and liver disease patients.

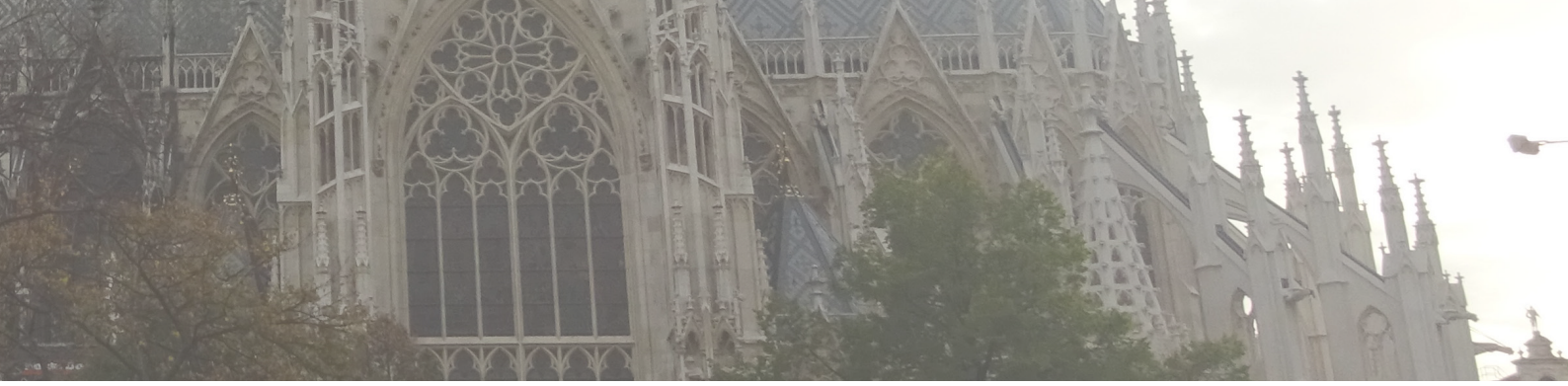
"Current models for healthcare delivery in Europe are unsustainable, with a rapidly ageing population, volatile political and economic landscapes as well as a shrinking workforce, and increasing lifestyle diseases," said Prof Michael Farthing, UEG President. "If we do not start planning for change now, we are all going to be facing a pretty uncertain future."

Responding to the current drain on European healthcare resources caused by gastrointestinal (GI) diseases, a collection of plausible, relevant, and challenging scenarios which could influence GI healthcare delivery in 2040 has been jointly discussed by UEG's Future Scenarios Working Group and specialist scenario planners over the last year. Designed to encourage a collaboration amongst the gastroenterology community to help construct a healthier future for patients, the three scenarios - Ice Age, Silicon Age, and Golden Age – may mould European healthcare by 2040, according to Prof Farthing.

Ice Age ominously predicts the collapse of the European Union (EU), the division of Europe into rich and poor, and the fall of European healthcare by 2040. This would be preceded by the initiation of two-tier medicine, caused by climate change, natural source depletion, and an ageing population, coupled with an exodus of doctors seeking cutting-edge treatment practice.

Silicon Age describes how evolution of technology, science, and social interaction will eventually cause comprehensive automation of diagnoses, therapies, and redirected health behaviour, leading to a Europe fuelled by e-economy and extensive e-health by 2040. Doctors would help patients to navigate and understand their personal electronic patient cloud records, while the rise of social media and a booming population would catalyse a worldwide acceptance of technology with the EU, contributing to European healthcare modernisation.

Promising outlooks result from an increased influx of immigrants and cross-border movement by Europeans, creating a so-called United States of Europe that seamlessly blends together education, taxation, and legislation; continuing a traditional duty of providing patient-centred care with cost-effective e-health platforms. This makes the Golden Age the brightest scenario of all - a powerful, highly organised, and united Europe that provides high quality, cost-effective healthcare to all European citizens by 2040.



Warning lights flash for GI control in Europe

Eastern Europe is in a dire condition, with 1-5-month survival post-diagnosis of major GI conditions, and GI disease prevalence is usually worst here.

GASTROINTESTINAL (GI) disorders in Europe present a longstanding and complex problem for clinicians and patients alike, with most of the continent far behind in experience and understanding of the growing epidemic.

Strategies in guiding relevant organisations on future clinical facilities and research priorities are determined by correct and up-to-date information on the GI disease burden in Europe, the availability and quality of diagnostic and medicinal services, and the effect of GI diseases in European Union member countries. Calculation of the course of the morbidity and mortality of digestive diseases will greatly influence the establishment of future health services and the construction of effective arguments supporting investment in research for hitherto unknown areas.

The UEG Council accepted a proposal from the UEG Future Trends Committee to commission an extensive survey detailing European-wide digestive health, released in May 2014 as '*White book report: Survey of Digestive Health Across Europe: final report*.' The final review is split into two parts: Part 1, '*The burden of gastrointestinal diseases and the organisation and delivery of gastroenterology services across Europe*', and Part 2, *'The economic impact and burden of digestive disorders'.*

Gastroenterology is a field that draws relatively small charitable research funding compared to other areas and has a relatively small focus in terms of policy. The review is intended by UEG to increase political and public awareness of all major GI conditions in Europe. This is done through evidence compilation and delivery of up-to-date information regarding the burden of GI conditions on public health, their economic impact (including patient health-related quality of life), and the assembly and provision of gastroenterology facilities around Europe.

Eastern Europe is in a dire condition, with 1-5-month survival post-diagnosis of major GI conditions, and GI disease prevalence is usually worst here. Future healthcare delivery has been shaped by increasing incidence of most GI conditions throughout Europe. The elderly suffer the highest rate of many GI conditions - an ominous indication of an ever-growing epidemic accompanying the ever-rising average age of Europeans.

Worryingly, there are few data describing the economic impact of GI conditions across much of Europe, although a continental trend illustrates the financial burden of inflammatory bowel disease. Future research is required that will study incidence, prognosis, and public health burden of numerous GI conditions in Europe.

Colorectal cancer: the next treatment chapters

VARIOUS therapeutic avenues, such as early adjuvant treatment, expression of certain prognostic factors, and increased interval cancer (IC) detection, have led to potential new approaches in the treatment and diagnosis of colorectal cancer (CRC).

For improved survival, it was recommended that CRC patients receive adjuvant treatment no later than 12 weeks after resection. This conclusion was reached by Dr Subramanian Nachiappan, St. Mark's Hospital and Academic Institute, Harrow, UK, who utilised hospital data from >200,000 CRC patients, who underwent surgery in the UK, over a 5-year duration.

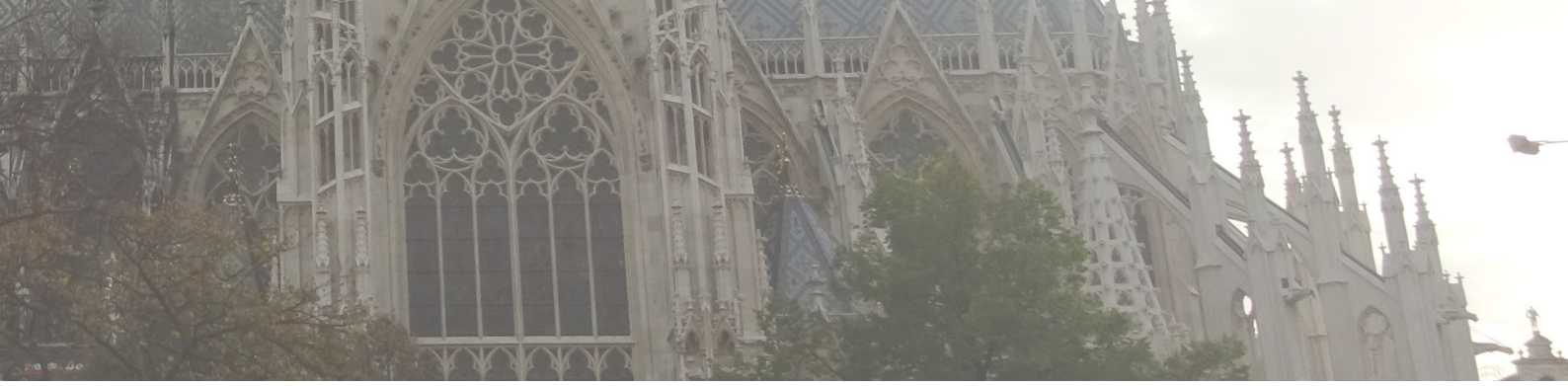
"This study offers strong evidence recommending that clinicians start adjuvant therapy as soon as possible – ideally within 8 weeks. In patients who may have had complications or a re-operation, 12 weeks may still be appropriate given that there is still a survival advantage. Rapid access and systemic logistical issues can be optimised to minimise a delay to starting chemotherapy," said Dr Nachiappan.

Evasion of the immune system's surveillance is paramount for cancer cell development; +3187G allele of human leukocyte antigen G (HLA-G) is associated with higher levels of soluble HLA-G protein, increasing the immune tolerance of cancer cells.

According Dr Marica Garziera, Aviano National Cancer Institute, Aviano, Italy, further investigations into the prognostic role of +3187G in a large population of CRC patients are to come, along with an analysis of eight other polymorphisms of the HLA-G gene, which may correlate with the adjuvant chemotherapy.

High expression of potential biomarkers, such as adrenomedullin receptor and calcitonin-receptor-like-receptor, has attracted interest since they can potentially predict CRC advancement and lymph node metastasis. They could also be used as biomarkers or for targeted inhibition therapy in the future. Finally, screening of IC – cancer diagnosed after the initial test but before the next screening test – with the utilisation of faecal immunohistochemical tests for haemoglobin could potentially increase cancer detection through regular screening.

> "This study offers strong evidence recommending that clinicians start adjuvant therapy as soon as possible – ideally within 8 weeks."
>
> *Dr Subramanian Nachiappan, St. Mark's Hospital and Academic Institute, Harrow, UK*



Digging deeper into Crohn's disease

Not all patients undergoing abdominal scanning for suspected obstructions will need surgery, thanks to the high sensitivity of dual-energy computerised tomography.

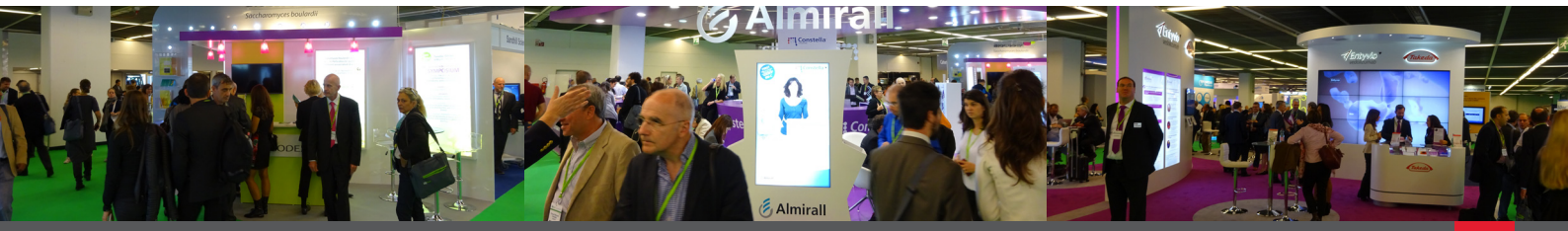
MANAGEMENT of Crohn's disease (CD) has been the focal point of several investigations in areas such as the long-term impact of steroid use, effectiveness of adalimumab therapy for small bowel stricture, and scanning techniques used to visualise and potentially differentiate between abdominal obstructions.

It was previously thought that the use of steroids was responsible for hindering growth in paediatric patients, which generated increased apprehension, but it was later revealed that growth hindrance can, in fact, be attributed to inflammation. In a recent study involving 75 CD patients, 29% failed to reach their final target height, and it was revealed that growth velocity was only negatively correlated with C-reactive protein and orosomucoid, further emphasising that steroid exposure did not have a role in growth hindrance.

New light is being shed on CD patients with small bowel stricture treated with adalimumab therapy, revealing that, in a study involving 97 patients, adalimumab failure occurred in 36% of patients at 12 months and 53% of patients at 18 months. Further analysis of predictive factors is underway.

Not all patients undergoing abdominal scanning for suspected obstructions will need surgery, thanks to the high sensitivity of dual-energy computerised tomography. Using this visualisation technique, 39 intestinal lesions were identified in 25 patients, 6 of whom needed surgery. According to Dr Tomer Adar, Shaare Zedek Medical Center, Jerusalem, Israel, this technique has a predictive value of 88% for determining which patients will not need surgery.

Another technique, contrast-enhanced ultrasound, is capable of distinguishing between phlegmons and intra-abdominal abscesses, correctly identifying lesions in 19 of 22 patients (86%) and further confirming final diagnosis at clinical follow-up. In the opinion of Dr Emma Calabrese, University of Rome 'Tor Vergata', Rome, Italy, this could potentially be used as a point-of-care technique to quickly distinguish between phlegmons and abscesses, thus improving the overall management of CD.



Faecal microbiota transplantation: a brave new therapy for combating *C. difficile* infection

FAECAL microbiota transplantation (FMT) has emerged as a highly effective treatment for recurrent *Clostridium difficile* infection and has been recommended in European treatment guidelines.

FMT involves the harvesting of healthy microbiota from a donated stool sample, which is then transplanted either by colonoscopy or enema into the intestine of the recipient to restore the natural gut flora composition, overcoming the toxic effects of *C. difficile* infection.

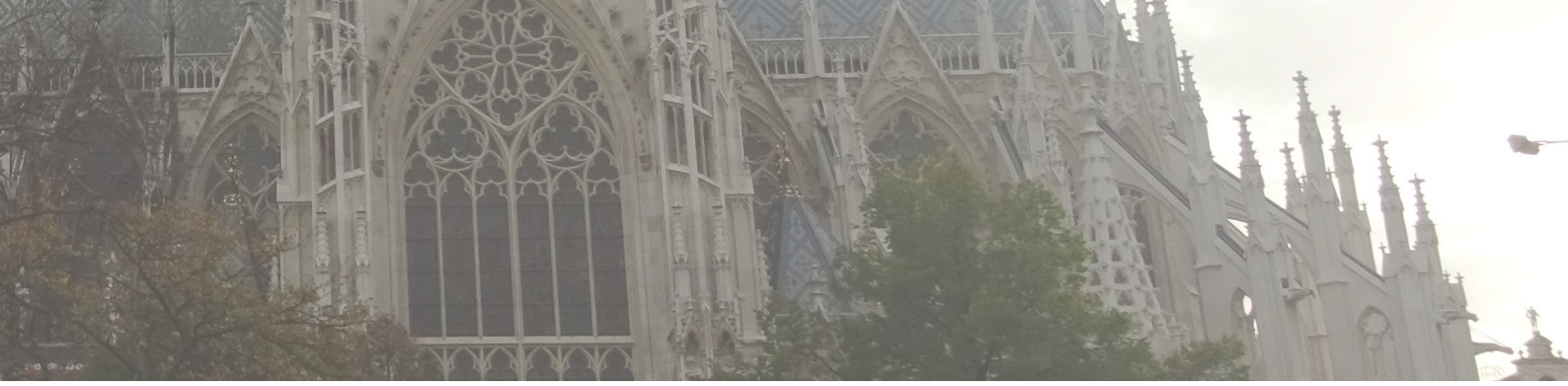
In the view of Prof Antonio Gasbarrini, Department of Internal Medicine, Gemelli University Hospital, Rome, Italy, FMT is gaining much-needed attention and has the capabilities of reducing both clinical and economic burdens of microbiota conditions. He also stressed that recurrent *C. difficile* infection is difficult to treat, but the advantages of this procedure includes a good safety profile and allows for the eradication of bacteria in approximately 90% of cases.

C. difficile infection has gained a grave reputation as the most common cause of hospital-acquired diarrhoea and is associated with significant morbidity and mortality in hospitalised patients. Elderly patients (>65 years) account for three-quarters of the cases. There have also been startling reports of emerging new strains, increasing antibiotic resistance, and increasing infections occurring outside of healthcare settings.

"Recurrent *C. difficile* infections are particularly difficult to treat, with long courses of antibiotics further disrupting the normal gut microflora, putting the patient at great risk of serious complications such as sepsis or perforation of the bowel," said Prof Gasbarrini. "There is an urgent need for more effective treatments for recurrent *C. difficile* infections and FMT is definitely one of them."

FMT is deemed highly effective and safe; it was once considered to be a last-resort option but it is now recognised for the treatment of recurrent *C. difficile* infections. "FMT can be considered a very simple form of organ transplantation that does not require immunological matching of donor and recipient and does not need immunosuppression after the procedure," said Prof Gasbarrini.

"I am delighted that FMT has now been formally recognised as an effective treatment for recurrent *C. difficile* infection and I hope the technique will now be used more widely in an effort to relieve some of the burden of this troublesome infection," Prof Gasbarrini added.



Pills providing the solution for hepatitis C relief

IMMINENT European-wide availability of two new pill-only treatments, which quickly cure most genotype 1 hepatitis C virus (HCV) sufferers, may lie just around the corner.

"These new pill-only regimens have the potential to offer more effective, safer, and faster virus eradication than current therapies, even in traditionally hard-to-cure patients," said Prof Michael P. Manns, Hannover Medical School, Hannover, Germany. "We hope that a pill-only regimen will encourage more people to come forward and accept treatment so we can one day eradicate this deadly virus."

Combining drugs has, until recently, been the standard of care for chronic HCV genotype 1 infection; however, this was linked to severe side-effects and included complex injection and tablet therapies for up to 1 year. Although effective, these treatments are difficult to manage and patient tolerability is often poor, deterring clinician use according to Prof Manns; therefore, a simpler, less toxic alternative is in demand.

Various combinations of oral antivirals for treating patients with chronic HCV genotype 1 infection were tested in two recent studies. 645 subjects with HCV genotype 1b infection enrolled in the HALLMARK-DUAL study, receiving an NS3 protease inhibitor twice-daily plus NS5A replication complex inhibitor or placebo once-daily. 12 weeks following the conclusion of a 24-week treatment period, the combination therapy delivered a sustained virological response (SVR) – deemed a cure - in 90% of previously untreated subjects and 82% of subjects who were unable to respond to, or could not tolerate, their previous regimen. "This is a vast improvement over standard triple therapy, with efficacy observed across the board – even in patients with liver cirrhosis and those who have failed other treatments," explained Prof Manns.

167 subjects with HCV genotype 1a and 1b infection were randomised in the COSMOS study, being treated with a second-generation NS3/4A protease inhibitor once-daily plus a NS5B polymerase inhibitor (with or without ribavirin) once-daily. Following a 12-week treatment period, 93% of subjects, including cirrhosis sufferers and interferon non-responders, had attained SVR.

"The results from these two studies suggest that interferon and ribavirin-based treatment for chronic HCV infection may soon become a thing of the past," said Prof Manns. "With several more pill-only regimens having also been reported this year, this is a key moment in the history of HCV treatment and represents an important step towards universally effective, needle-free treatments for HCV."

Mighty mechanisms of pancreatic cancer unearthed

GREAT strides have been taken in understanding the role of inflammation in pancreatic cancer (PC) development through the discovery of four key carcinogenic processes, opening the way to more effective future treatment.

The parasympathetic nervous system is influential in PC onset; this was proven when PC cell lines were treated with parasympathomimetic agents in a mouse xenograft model, triggering a large dose-dependent decrease in tumour growth, invasiveness, and levels of intracellular p44/42 mitogen-activated protein kinase (MAPK) phosphorylation. Therefore, suppression of the p44/42 MAPK pathway appears key in inhibiting PC cell proliferation and invasiveness by the parasympathetic nervous system.

The inflammatory capability of macrophages may be stunted by PC cells. A series of *in vitro* studies showed that pro-inflammatory Type M1 macrophages and anti-inflammatory Type M2 macrophages stimulate increased cell migration from primary and metastatic pancreatic adenocarcinomas, respectively. Increasing inflammatory cytokine expression with interleukin (IL)-6 or IL-4+ lipopolysaccharide stimulation could partially or completely reverse PC cell invasion. "Our study shows that the invasiveness of PC cells increases in the presence of both pro and anti-inflammatory macrophages when cultured in medium simulating the *in vivo* extracellular matrix environment," said Dr Aino Koski, Helsinki University Central Hospital, Helsinki, Finland.

ATM gene expression adversely affects PC progression; the gene produces a tumour suppressing effect in pancreatic ductal adenocarcinoma. Results in a mouse model illustrated how the *ATM* gene removal boosts precursor proliferative acinar-to-ductal metaplastic lesions, pancreatic intraepithelial neoplasias, and fibrotic reactions compared to controls, and were also associated with epithelial-to-mesenchymal transition (EMT) following ductal reprogramming.

Inflammation-induced transcription factor NFATc1 was shown to fuel EMT programming and preserve stemness via Sox2-dependent transcription in tumour cells from mouse and PC models. The relative activity of p53 and NFAT1c may play a role in regulating the balance between epithelial cell preservation and conversion into a dedifferentiated cancer cell.

"Our study shows that the invasiveness of PC cells increases in the presence of both pro and anti-inflammatory macrophages when cultured in medium simulating the *in vivo* extracellular matrix environment."

Dr Aino Koski,
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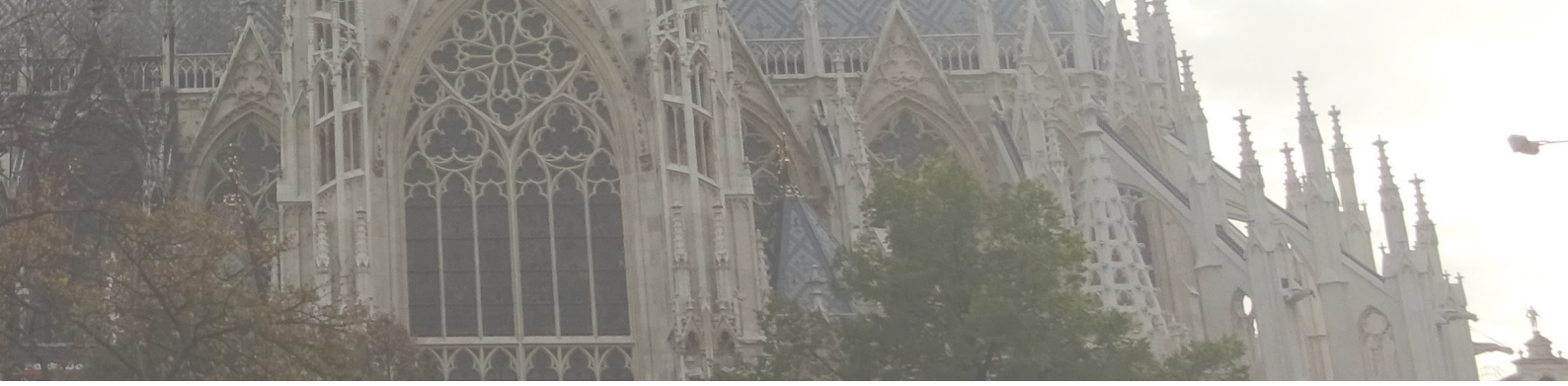


Psychological blow of IBD highlighted in the young

IMPACTS of inflammatory bowel disease (IBD) upon young people have been assessed in a campaign studying the psychological effects of the condition, including influences upon education and future employment.

A range of disadvantages were found to be associated with IBD in young people during the UEG IBD in Children Media Campaign; this occurred simultaneously with European-wide public exams and University schedules, being supported by a social media campaign which attracted a support base of an estimated 128,000.

The average diagnosis age was found to be 11.9 years, with 30% of total patients presenting with IBD between 10 and 19 years of age; children with IBD were often deemed emotionally vulnerable. As not all patients present with the most common symptoms, diagnosis of IBD can be difficult; 17% of under 18s wait >5 years to undergo a final diagnosis. This can cause a major blow to a patient's mental wellbeing and ability to plan for their future.

Depression affects up to 25% of young people with IBD, comprising a range of paediatric mental defects including behavioural problems, psychiatric disorders, and reduced social competence. This highlights the need for faster diagnosis and greater psychosocial support for those affected. The ramifications of IBD extend to the classroom, with up to 3 months of school absenteeism reported among children with IBD every year. 61% of under 18s felt that IBD prevented them from achieving their full educational potential.

Major medical media in Europe were used to alert healthcare professionals of the need to encourage patients to seek support in overcoming any mental issues they may experience, such as depression, alongside the campaign. A gulf exists between European countries regarding training provisions and healthcare professional resources, posing a significant obstacle to screening uptake, triggering the UEG to call for increased nurse endoscopy training.

It is time to stop inequality in gastrointestinal medicine!

WORRYING disparities in the provision of healthcare services for patients suffering gastrointestinal (GI) and liver diseases have been revealed across Europe.

Changing trends concerning GI disorders and deliverance of care have led to a call for increased public and political awareness to improve patient service provision and support after The Survey of Digestive Health Across Europe found major differences in long-term health outcomes.

"We are particularly concerned about the increasing incidence of most major GI disorders across Europe and the clear differences in outcomes for patients between Eastern and Western nations," said Prof Michael Farthing, UEG President.

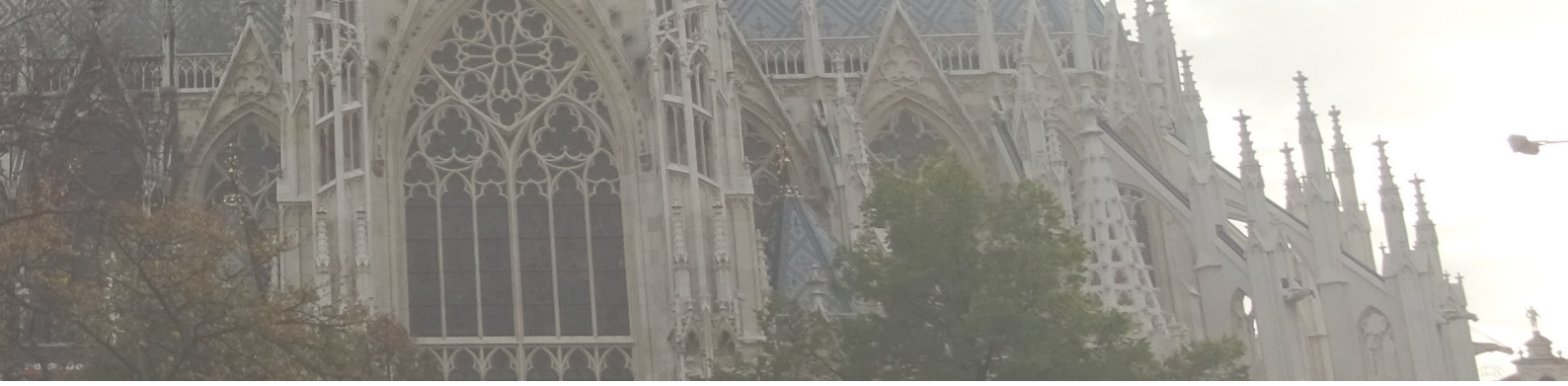
The research group, from Swansea University, Swansea, UK, used several research methods in the two-part study (including systematic review, meta-analysis, and geographic mapping) to assess digestive health across the continent; peer reviewed journals, grey literature, reports, websites, and other data resources were all used.

The findings revealed several trends in the prevalence and incidence of GI disorders. Numerous countries in Europe have seen significant increases in the incidence of GI-related health issues, such as upper GI bleeding, coeliac disease, and colorectal cancer (CRC). Furthermore, prevalence rates were seen to be greater in many Eastern European countries when compared with other regions; mortality from GI disorders was highest in Eastern and North Eastern countries and lowest in parts of Scandinavia and the Mediterranean Islands.

GI cancers, in particular, were revealed to present a significant issue; they are now the leading cause of cancer death in Europe. Yet whilst mortality rates have fallen for CRC over several decades in nearly all Western, Northern, and Central European countries, results showed that they continue to climb in many parts of Eastern and Southern Europe.

Regarding the healthcare provisions currently implemented for CRC patients, screening programmes are now in place in the majority of European countries; however, there is no standardised approach to these, and participation in them is divided. Similarly, upper GI bleeding is managed in different ways across Europe, with a lack of consensus on best practice; endoscopy services are irregular and not currently seen as a priority by policymakers, which could seriously impact upon future service demands.

"Our hope is that, ultimately, the survey and the reports generated will help to improve care and health outcomes and reduce inequalities across the continent," concluded Prof Farthing.



Dynamic duo carry torch for future CRC screening

TWO blood-borne biomarkers could be the key to successful future colorectal cancer (CRC) screening, potentially boosting critically low compliance levels through a non-invasive and cost-effective procedure.

Rising from an overall disappointing crop of cancer biomarkers, abnormal DNA methylation patterns and small, non-coding RNAs, known as microRNAs, are both instrumental in the carcinogenic process. The former may comprise a prime DNA-based screening biomarker, particularly abnormal Septin9, while the latter can discriminate between different types of CRCs with only a small number required to paint a vivid picture of cancer cell processes. A promising future is possible for both, as their presence in plasma opens the door to a simple blood test that would trigger elevated compliance and possibly save thousands of lives.

"Blood-borne biomarkers are opening up exciting avenues of investigation in colorectal and other cancers," said Dr Antonio Castells, Institute of Digestive Diseases Hospital Clinic, Barcelona, Spain. "We now have a better understanding of the molecular events participating in the development of CRC and these provide valuable targets for both the early detection of CRC and the development of novel treatments."

Stool tests and structural examinations, the most popular current CRC screening methods, are implemented for cancer and pre-malignant lesion detection, and have proved both effective and cost-effective in the average-risk population. However, compliance is very low, adversely affecting test efficacy.

Despite high hopes, methylation markers have delivered mixed results in trials. In preliminary studies CRC and adenoma sensitivity was very high, ranging between 70-90% in patients. However, expectations took a tumble upon conclusion of the 1,500-strong PRESEPT study, which evaluated a well-studied marker, Septin9. The average sensitivity rate measured 50%, with Stage 1-3 sensitivity averaging 45%.

Having delivered a spate of positive results, including an overall sensitivity of 75-90% in a major study, miRNAs are slightly further ahead in the race. A plethora of advantages accompany the molecule: miRNA dysregulation is an early event in advanced CRC and early stages of advanced adenoma, and are also very stable in a range of biological fluids, including blood. This means that abnormality can be detected easily and early on in cancer pathogenesis.

"Both of these potential new CRC screening approaches have shown promise in preliminary studies and should be explored further in larger cohorts of patients," concluded Dr Castells.

Autoimmune pancreatitis management in mouse models

UNEXPECTED new treatment options could help to regulate autoimmune pancreatitis (AIP), a rare form of chronic pancreatitis, for which long term management has been limited in the past.

AIP is a difficult disease to say the least, with the only therapy to have been established (corticosteroids) presenting significant relapse rates (15-60%). In the past, it has been demonstrated by research that acinar specific lymphotoxin expression in mice induces autoimmunity with features reminiscent of human AIP, and in contrast to corticosteroids, which only diminish inflammation, inhibition of lymphotoxin beta receptor signalling (LTβR-Ig) completely overturns autoimmunity.

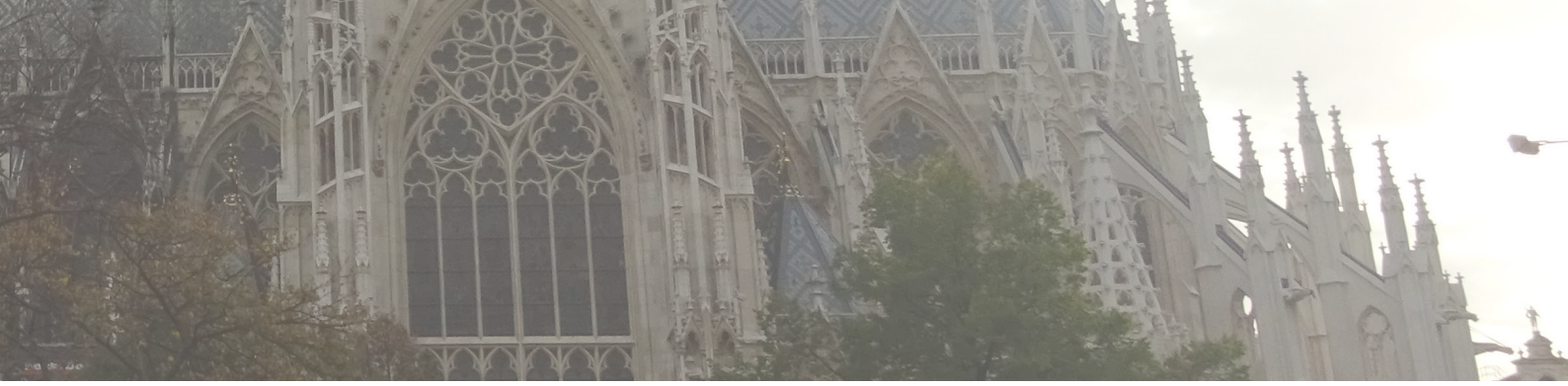
Now new research has emerged, investigating the effectiveness of inhibiting the LTβR pathway when compared to the exhaustion of a subset of immune cells, which are suggested to play a pathological role in AIP progress.

Mice with AIP were treated with anti-CD20 monoclonal antibody (mAb) (Rituximab), anti-CD4 mAb, and LTβR-Ig fusion protein. They were further tested in regards to autoantibody production, histology, tertiary lymphoid organ (TLO) integrity, cytokine and chemokine expression, and other organ involvement in the kidneys, before being compared to LTβR-Ig treatment. Macrophage and T helper cell polarisation were also evaluated during different treatments.

It was seen that LTβR-Ig and anti-CD20 treatment led to a decrease in autoantibody production, inflammatory cell infiltration in the pancreas, and extrapancreatic manifestation in the kidneys; the molecular mechanism of this beneficial effect could potentially involve the downregulation of Stat3 and non-canonical NF-κB activation. As well as this, unlike anti-CD20 and anti-CD4 treatments, blocking LTβR signalling reverted acinar cell proliferation and acinar-to-ductal metaplasia formation, disrupting the formation of TLOs. Anti-CD4 treatment resulted in reduced Th1 and Th2 cell polarisation, yet this did not alleviate AIP.

It is with this mouse model that researchers are stating that therapy with LTβR and anti-CD20 antibody is superior to anti-CD4+ T cell depletion; these targeted therapies highlight new anti-inflammatory and anti-autoimmune mechanisms, and indicate that inhibiting the LTβR-Ig pathway could become an alternative or additional approach to AIP treatment.

Further research may be required before the treatments can make it to trials in humans; however, there is no denying the promise of this therapy as a potential future treatment for a rare and lingering disease.



CORTIMENT®: standing up to ulcerative colitis

A PROMISING treatment, CORTIMENT® MMX® (budesonide), for the induction of remission in patients with active, mild-to-moderate ulcerative colitis (UC), has been granted marketing approval across 27 European Union countries. This drug could be a potential saving grace for UC sufferers, filling the void left by current therapy.

> "Well over two million people in Europe suffer from UC. CORTIMENT, with its proven efficacy and safety profile, will provide an important new option for physicians treating active, mild-to-moderate UC."
>
> *Dr Simon Travis, Consultant Gastroenterologist, Oxford University and the John Radcliffe Hospital, Oxford, UK*

"Well over two million people in Europe suffer from UC. CORTIMENT, with its proven efficacy and safety profile, will provide an important new option for physicians treating active, mild-to-moderate UC," said Dr Simon Travis, Consultant Gastroenterologist, Oxford University and the John Radcliffe Hospital, Oxford, UK.

A form of inflammatory bowel disease, UC is characterised by inflammation and the development of ulcers along the inside of the colon. This long-term condition can cause symptoms such as cramping, bloating, diarrhoea, and weight loss, which can significantly impact on quality of life.

The condition has no cure, but its symptoms can be managed. Approximately 30% of mild or moderate UC sufferers are not sufficiently responsive to aminosalicylate drugs, and those who are responsive are also given systemically absorbed corticosteroid, whose success is limited by significant side-effects.

CORTIMENT is a locally acting corticosteroid in an oral tablet formulation which utilises MMX® multi-matrix technology for a controlled delivery of budesonide directly into the colon.

The 9 mg tablet is taken once-daily for up to 8 weeks by adult patients. Based on Phase III studies, it was revealed that patients were 2.4 to 3.9-times more able to achieve clinical and endoscopic remission when compared with their placebo counterparts. There were also no observable, clinically significant side-effects compared to placebo after the treatment period of 8 weeks.

The product is currently developed by Cosmo Pharmaceuticals SpA. In the USA, the drug is licensed to Salix Pharmaceuticals, Inc. under the brand-name of UCERIS®, while Ferring Pharmaceuticals, Inc. holds the licence for the majority of countries in the world, excluding Japan.

Cutting-edge CRC screening delivers superior survival and uptake

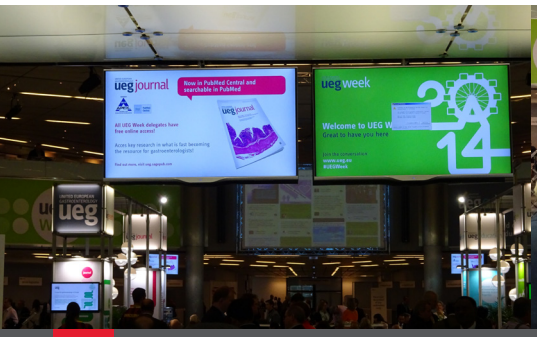
MORTALITY reductions for colorectal cancer (CRC) and boosted compliance for screening have been delivered through implementation of faecal immunochemical testing (FIT), a cost-effective and practical alternative to guaiac faecal occult blood test (gFOBT) that enables higher sensitivity readings, thus detecting a higher proportion of cancers.

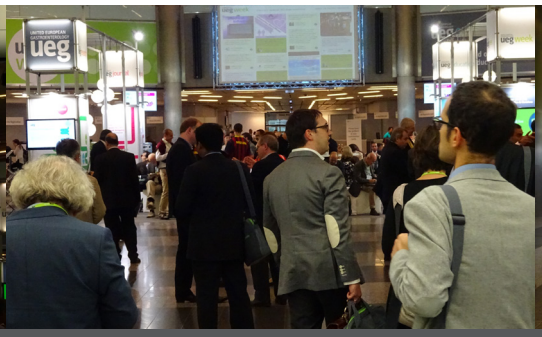
FIT is different to gFOBT, which measures the haem portion of haemoglobin. "We cannot measure haem so well, but what we can measure is the globin bit of haemoglobin; that is a protein and it is unique to humans. So [if] you measure globin, you know you are measuring blood from the human species, not some contamination from food," said Prof Stephen P. Halloran, Royal Surrey County Hospital, NHS Bowel Cancer Screening Programme, University of Surrey, Surrey, UK.

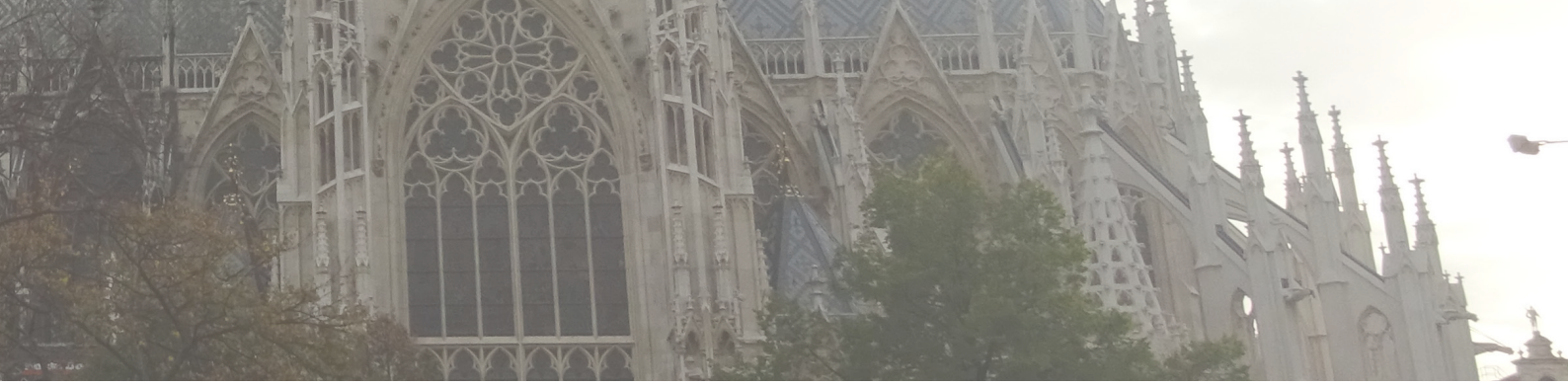
The effectiveness of FOBTs in reducing CRC mortality was demonstrated in large randomised controlled trials 20 years ago; this has proved the catalyst for countries to develop CRC screening programmes. The Bowel Cancer Screening Programme, taking data for screening uptake from 2007-2013, recorded a 61% uptake for CRC screening, including 20% of those who initially refused and 90% of those who previously accepted, in Southern England. This reveals room for improvement, as the number of cancers diminishes with every screening since cancers are removed every time.

FIT is a single test, but can be personalised by combining it with other parameters. Criticism of population-based screening programmes has been based on its seemingly impersonal nature; however, the internet may be used to communicate directly with individuals so that they may discover benefits and risks of screening. Furthermore, a quick response code, assigned after screening, allows individuals to track their results package via a personal account.

"We need to adopt FIT, that is the way to start; that is not to say that is the way it will be in 10 years or 15 years' time, there will be new products that come along, but if you have got a system and a structure, then you have got the essence of what will be a good screening programme. And I suggest that we might need to increasingly exploit the power of the internet to communicate with the population. Research needs to continue to see how we might be able to reach the impoverished population which generally is reluctant to screen," concluded Prof Halloran.





Call for personalised approach in primary care dyspepsia patients

MANAGING optimal dyspepsia demands a personalised approach, including individual risk assessments, in order to resolve current diagnostic issues.

Complex issues swamp the diagnosis and management of dyspepsia, one of the most common conditions seen by consultants in general practice, in primary care patients. Though the condition can present as an early sign of cancer, in most patients it is suffered only temporarily, and at present the only available method of ruling out more serious illness is to perform an upper gastrointestinal (GI) endoscopy. This procedure is often unpleasant for patients and should be avoided wherever possible.

In the past, gastroscopy rates have been stable, yet recent decades have seen dramatic changes in morbidity, which are linked to epidemiological developments surrounding acid-related and *Helicobacter* diseases. Thus, physicians are faced with the challenge of implementing personalised care for individual patients.

Sometimes, different types of upper GI disease can explain recurring symptoms of dyspepsia. 10% of patients present common alarm symptoms associated with stomach and oesophageal cancer (haematemesis, anaemia, and trouble swallowing), yet only 6% of these individuals will have cancer; therefore the value of alarm symptoms at predicting cancer is only 6%.

Alternatively, there is a 99% risk of having GI cancer without presenting alarm symptoms, making them a particularly useful tool in primary care; the risk of upper GI cancer in a case of dyspepsia presenting alarm symptoms is 1 in 20, authorising referral for endoscopy, whereas, in the absence of symptoms, the risk is <1%.

To complicate matters further, healthcare professionals must also account for functional dyspepsia, a syndrome that is left over when all other possible motivations have been dismissed, and discriminating between this and other functional GI syndromes is significantly difficult.

General practitioners (GPs) possess three diagnostic tools: acid reduction trials, *Helicobacter pylori* testing, and upper GI endoscopy. Yet, while some young patients presenting for the first time respond to a short course of antacids, others require a longer course of proton pump inhibitors, after which, symptom response must be assessed, and others still require full endoscopy.

Most gastroenterologists apply single management strategies for all chronic dyspepsia sufferers; it is no surprise then that, given the specific treatment requirements for patients with recurrent dyspepsia, a call for individual risk assessments of patients has been suggested.

Higher standards needed in diagnosing food intolerance

> "Hopefully, as clinicians and patients become more aware of the range of conditions associated with wheat and gluten, the quicker they can be diagnosed, receive the most appropriate treatment, and prevent associated health problems."
>
> *Prof Giovanni Gasbarrini, Catholic University of the Sacred Heart, Rome, Italy*

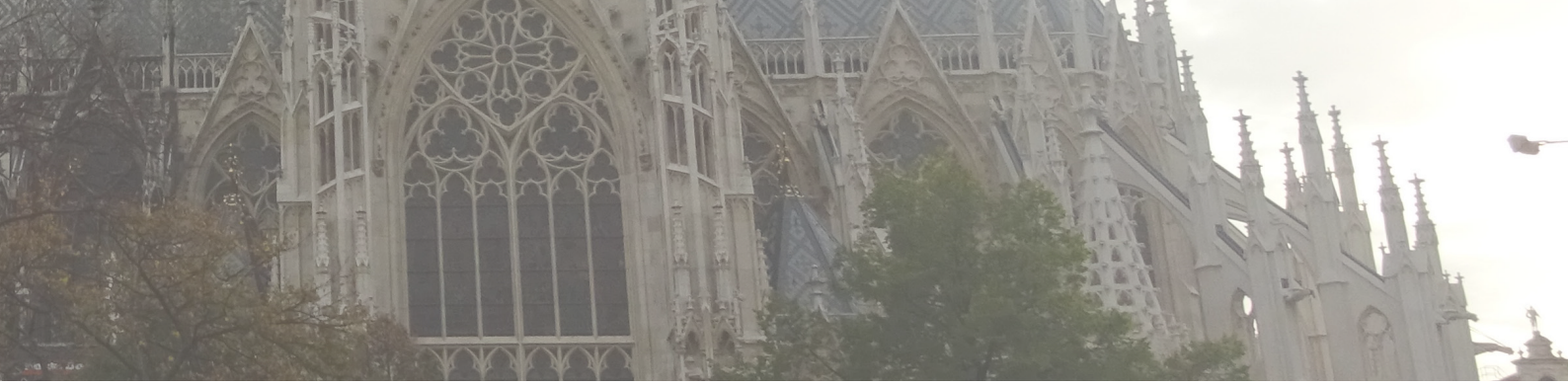
INCREASING numbers of individuals are found to be intolerant to everyday food sources, such as wheat in bread and cereal; experts are calling for greater awareness of these disorders so that they may be diagnosed and treated more efficiently.

Gluten is composed of the proteins gliaden and glutenin; the former protein is responsible for extensive medical conditions for anyone with intolerance, such as wheat allergy, coeliac disease, and non-coeliac gluten sensitivity.

Yet according to a recent paper by Prof Giovanni Gasbarrini and Dr Francesca Mangiola, Department of Internal Medicine, Catholic University of Sacred Heart, Policlinico "A. Gemelli" Hospital, Rome, Italy, those eating a gluten-free diet may also be at risk of developing food intolerances due to an excessive substitution of alternative carbohydrates and foods containing nickel.

Thus, the authors have offered practical advice on how to differentiate between coeliac disease and other gluten-related disorders to doctors, so that they may diagnose conditions more swiftly and effectively, ensuring that patients are not partaking in a gluten-free diet unnecessarily. Their main points for physicians are: to perform a thorough medical history, with extra attention given to the native gut microbiota; to explore symptoms and assess the presence of any allergy history; and to carefully evaluate genetic background – this is particularly important in targeting and confirming diagnoses.

Prof Gasbarrini explained: "Many clinicians struggle to differentiate between wheat-related disorders so practical advice like this is always helpful. Hopefully, as clinicians and patients become more aware of the range of conditions associated with wheat and gluten, the quicker they can be diagnosed, receive the most appropriate treatment, and prevent associated health problems."



Greater gastrointestinal understanding just a click away

ENHANCED e-learning has been delivered by UEG, which is leading the way towards improved international care and knowledge through a series of stimulating innovations aimed at the gastroenterology and hepatology communities. The unique education platform aims to shape the future of the two fields for the better.

"The strength and advantage of the UEG educational platform is that the UEG Member Societies and UEG National Society Members feed into it, shaping a unique and comprehensive portal with extensive gastrointestinal (GI)-related material and educational resources," said Dr Charles Murray, Chair of UEG's e-learning Taskforce.

Exponential growth has seen an influx of thousands of categorised and searchable documents, media clips, continuing medical education (CME) courses, and meeting content into the UEG e-learning portal. These resources allow the deployment of excellent, accessible, and independent education and training in gastroenterology. A wide range of activities are available, including training courses – both as e-learning and hands-on residential courses – while the UEG is hosting an enormous online library presenting the most up-to-date GI stories, which will inspire much debate and discussion.

> "UEG Education is at the beginning of an exciting stage in its development and we value input in shaping the future."
>
> *Dr Charles Murray, Chair of UEG's e-learning Taskforce*

UEG initiatives include describing translational and clinical studies across the entire gastroenterology universe, while Training Support provides funds for original training and educational programmes, as well as worldwide scientific and professional collaborations. EU Affairs seeks to influence construction of a successful European health policy through the promotion of research, prevention, and treatment of digestive diseases.

"UEG now look to improving their educational resources. We aim to do so by further engagement with Member Societies and National Societies through sharing of information, research, and news and look forward to any ideas from members and specialists. UEG Education is at the beginning of an exciting stage in its development and we value input in shaping the future," explained Dr Murray.

The changing face of coeliac disease

The only treatment for CD is a strict gluten-free diet; the impact of this on daily life can be detrimental, causing higher-than-average rates of depression.

CHANGES in the nature and number of incidences of coeliac disease (CD) across Europe have led to the roles of primary care professionals becoming central to the lives of >5 million people; once considered a rare condition, found only in children, CD is presently overturning years of medical assumption.

The condition can lead to small bowel inflammation, and has been associated with Type 1 diabetes. Past symptoms included weight loss and a failure to thrive in children, yet over the years, the nature of these has changed and now patients are just as likely to be recognised suffering from unexplained anaemia.

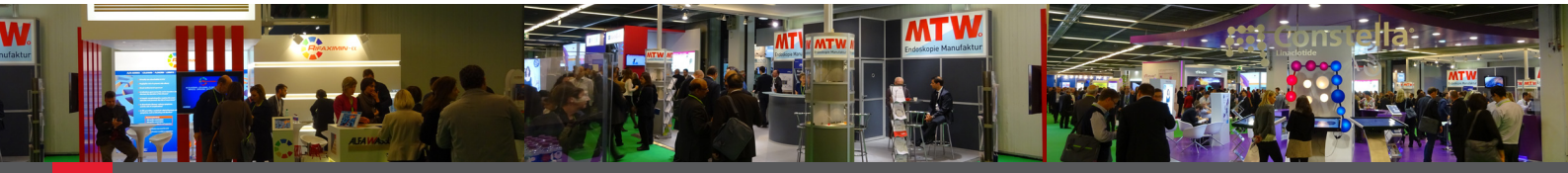
CD normally presents in those who are genetically predisposed, carrying tissue types Human Leukocyte Antigen (HLA)-DQ2 and HLA-DQ8, though only 1% of these individuals actually develop the condition. Yet while it is widely understood in terms of its immunological processes, researchers are unaware of what triggers the disease.

One hypothesis suggests that lack of exposure to infectious agents in early childhood hinders the immune system from developing properly; significant differences in the seroprevalence of CD recognised in a research comparison, between Finland and the Russian region of Karelia, support this. However, a complete demonstration of European-wide prevalence rates is yet to be achieved, and increases in incidence could be due to increased awareness and testing.

Perhaps one of the best ways to spot CD is to review irritable bowel syndrome (IBS) patients; UK research has found 25% of those previously diagnosed with IBS go on to develop CD. Peripheral neuropathy and ataxia sufferers may also carry coeliac antibodies, with the latter possibly benefiting from a gluten-free diet.

Approximately only half of CD sufferers receive diagnosis. Therefore, there is an urgent need to better equip medical professionals in recognising the condition. Serological tests may be accurately used for both adults and children; however, negative serology can be caused by reduced gluten levels at the time of testing. This has become a significant issue for patients undertaking a gluten-free diet before presenting in primary care.

This being said, the only treatment for CD is a strict gluten-free diet; the impact of this on daily life can be detrimental, causing higher-than-average rates of depression, and in the meantime, good dietary advice is required, along with patient support services to help manage the condition.



Doctors debate over *Helicobacter pylori* strategy

DISCUSSIONS concerning the treatment and management of *Helicobacter pylori* infection have featured in the Maastricht IV consensus report; experts have reviewed clinical data to prepare a preventative attack on the leading bacterial cause of stomach ulcers.

A test-and-treat strategy for unexplored dyspepsia where *H. pylori* prevalence is >20% has been suggested. The foundations of this strategy lie in non-invasive diagnostic tests which are widely available across Europe; the use of stool antigen tests (SATs) has been proposed, and age limits for such a strategy would vary across countries, based on local incidence rates of gastric cancer (GC) and alarm symptoms.

The use of proton pump inhibitors (PPIs) may have important implications for everyday practice; guidelines stress that long-term PPI treatment in *H. pylori* patients accelerates the development of atrophic gastritis, yet the eradication of *H. pylori* in extensive PPI treatment prevents atrophic gastritis onset in animal models.

Eradicating *H. pylori* not only decreases the risks of peptic ulcers and GC, but also avoids the need for endoscopic procedures and diminishes dyspepsia symptoms in approximately 10% of patients. However, further research is needed to comprehend individual host reactivity.

In managing *H. pylori*, it was declared that SATs using monoclonal antibodies have high accuracy rates for both initial and post-treatment diagnosis of infection, despite the fact that in-office SATs are not as reliable. Developments in this area might bring about wider acceptance amongst practitioners of the test-and-treat strategy in countries with high prevalence.

Treatment methods have also been assessed. Growing resistance to clarithromycin has led to changes in treatment methods – while standard triple therapy used to have a high cure rate, it is no longer always appropriate. Therefore the experts recommend different strategies for low and high clarithromycin resistance.

It has been confirmed that lengthening the duration of PPI-clarithromycin-containing triple treatment from 1 to 2 weeks improves eradication efficacy, but leads to diminishing levels of compliance and higher costs, which can impact upon success rates.

Finally, experts state that although environmental factors may influence the development of GC, most of these only become risk factors if *H. pylori* are present, and are inferior to the effects of the bacterial infection. Management of *H. pylori* should thus have a local approach, and so far no county has adopted public health measures to treat those infected or protect populations at risk.

Link between depression and irritable bowel syndrome

IRRITABLE bowel syndrome (IBS) patients who are suffering from anxiety and depression process pain signals from the gut abnormally, clarifying the tempestuous relationship between psychological factors and IBS symptoms.

A study presented by Prof Sigrid Elsenbruch, Professor of Experimental Psychobiology, University of Duisburg-Essen, Essen, Germany, highlighted that in a central pain inhibition model during placebo analgesia, depression contributed to abnormal pain processing in IBS patients while anxiety did not.

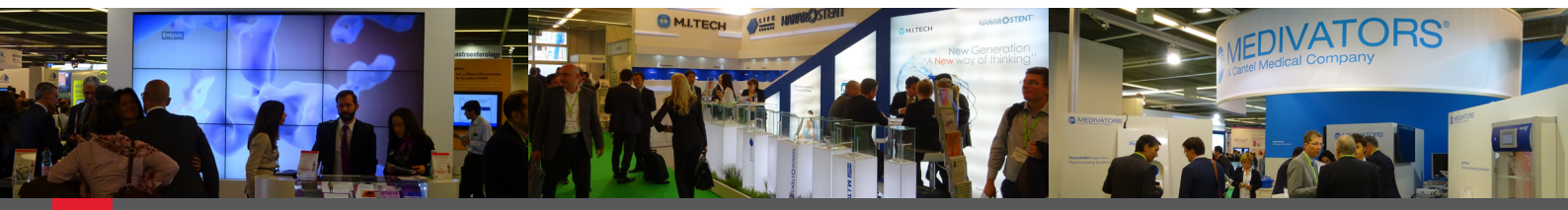
"Our study has shown that patients with IBS are less able to suppress pain signals in the brain coming from the bowel and that depression plays a role herein," said Prof Elsenbruch. "This study confirms the complex relationship between the gut and the brain and shows that affective disorders may contribute to the development or maintenance of disturbed pain processing in IBS."

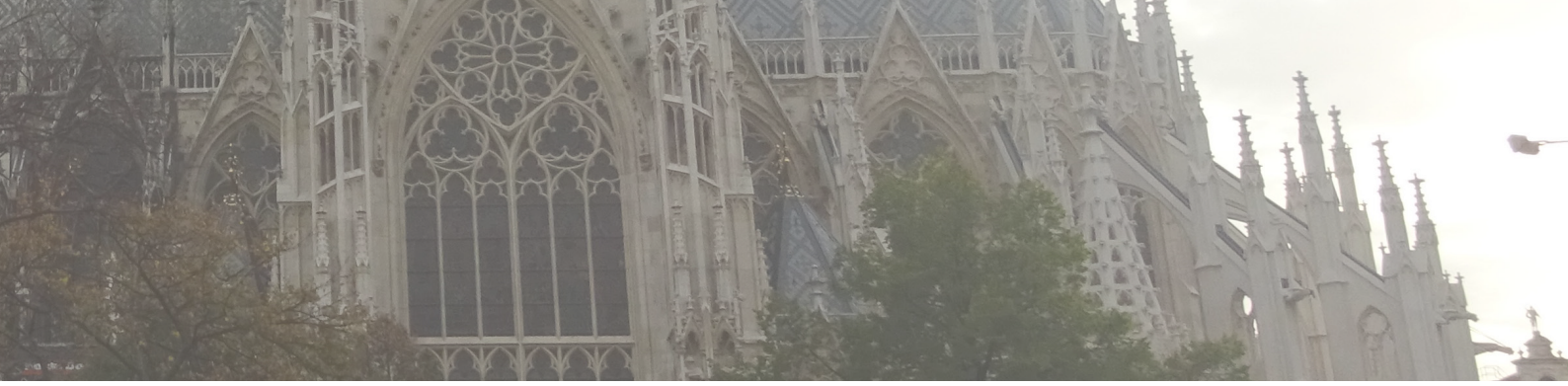
The most common functional gastrointestinal disorder, IBS can cause a combination of recurrent bouts of abdominal pain, bloating, diarrhoea, and constipation. Due to this discomfort and inconvenience, patients tend to also suffer with depression and anxiety. A study has revealed that 38% of IBS patients had clinical depression in comparison to 6% in healthy patients, and 32% suffered from anxiety in comparison to 13% reported in their healthy counterparts.

The role of the central nervous system mechanism along the 'brain-gut' axis in IBS has come under scrutiny for further answers regarding this significant link. Studies have shown that neural processing of visceral stimuli is altered in IBS, where these patients tend to have lowered pain thresholds. To test this theory, the latest study included the induction of painful rectal distensions using a pressure-controlled barostat system in 17 IBS patients and 17 healthy controls, matched in both gender and age.

Functional magnetic resonance imaging was used to assess the neutral activation in pain-related brain areas while subjects received sequential intravenous administrations of saline and an anti-spasmolytic drug (but the latter was also a saline placebo) to observe the activation patterns in normal placebo pain response.

There was reduced neutral activation in pain-related brain areas in both saline and sham treatments (placebo) in healthy participants which indicated that there was significant central pain inhibition. This was not observed in the IBS patients, suggesting that there is a deficiency in central pain inhibitory mechanisms in IBS.





Hands-off approach to alcoholic liver disease diagnosis

FUTURE of alcoholic liver disease (ALD) diagnosis is shifting away from current invasive diagnostic methods to the use of non-invasive serum biomarkers, signalling a step-up in the battle against one of the most prominent types of liver disease in Europe.

147 subjects (40 females, 107 males) with ALD and 30 controls enrolled in a study that aimed to decipher the serum profile of selected biomarkers of three cooperative processes in ALD pathogenesis, i.e. inflammation, angiogenesis, and adipose tissue secretion (adipokines). The most effective diagnostic biomarkers for ALD complications were shown to be frequency of Th17 cells as well as Ang2 and Acrp30 concentrations, although complex statistical models involving numerous parameters from various pathways in ALD pathogenesis provided predictive power surpassing that of either biomarker alone.

Subjects were divided into subgroups based on gender, severity of liver dysfunction according to the Child-Turcotte-Pugh and model for end-stage liver disease scores, and the existence of ALD difficulties at the time of hospital admission. T cell phenotype was determined through use of a FACSCalibur flow cytometer (Becton Dickinson, USA) with CellQuest software; CD3+CD4+IL17+ cells were considered Th17 and CD4+CD25+FOXP3+ Tregs, and were expressed as the percentage of total CD3+CD4+ and CD4+CD25+ lymphocytes, respectively. Immunoenzymatic enzyme-linked immunosorbent assay tests were used to evaluate serum levels of angiogenic biomarkers and adipokines.

Frequency of Th17 cells and elevated Ang2 levels in plasma of ALD subjects appear to be instrumental in ALD patient survival, proving to be independent predictors of mortality (Th17) and of severe liver dysfunction and ALD complications, including development of ascites, encephalopathy, renal dysfunction, and death (Ang2), respectively. 12 of 147 subjects died in the 90-day follow-up, while Th17 and Treg balance adjustment was seen in the most critically ill subjects. Plasma concentrations of vascular endothelial growth factor, Acrp30, and resistin were also far greater compared to controls, with Acrp30 linked independently to severe liver dysfunction, development of ascites, and hepatic encephalopathy.

The most effective diagnostic biomarkers for ALD complications were shown to be frequency of Th17 cells as well as Ang2 and Acrp30 concentrations.

UEG WEEK ANNUAL CONGRESS 2014

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UEG WEEK 2014 AWARDS

UEG LIFETIME ACHIEVEMENT AWARD

Prof Christoph Beglinger,
Switzerland

Responsible for great strides in understanding the role of peptide hormones in digestion and eating control, while playing a key part in modern reorganisation and progression of UEG's scientific programme.

UEG RESEARCH PRIZE

Prof Rebecca Fitzgerald,
UK

Combination of quantifiable genomic assays with a patient-friendly non-endoscopic cell retrieval device called Cytosponge™ for management of patients with Barrett's oesophagus.

TOP ABSTRACT PRIZE

Dr Jochem Bernink,
the Netherlands

Human mononuclear phagocytes regulate the balance between intestinal group 1 and group 3 innate lymphoid cells.

Dr Lidewine Daniels,
the Netherlands

A randomized clinical trial of observational versus antibiotic treatment for a first episode of uncomplicated acute diverticulitis.

Dr Takahisa Matsuda,
Japan

Randomized comparison of surveillance intervals after colonoscopic removal of adenomatous polyps: the Japan polyp study.

Dr Gitta Maria Seleznik,
Switzerland

Lymphotoxin promotes acinar cell reprogramming and accelerates pre-neoplastic conversion in KRAS-induced pancreatic tumorigenesis.

Dr Michael Sigal,
USA

Helicobacter pylori alter stem cell homeostasis by direct colonization of the gastric glands.

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HIGHLIGHTS FROM THE UEG WEEK CONGRESS 2014: NEW EVIDENCE AND NOVEL THERAPIES FOR IRRITABLE BOWEL SYNDROME

***Caroline Charles,[1] Enrico Stefano Corazziari[2]**

1. Scilink Medical Writing, Biarritz, France
2. Internal Medicine and Medical Specialties, "Sapienza" University of Rome, Rome, Italy
**Correspondence to scilink.mw@gmail.com*

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ABSTRACT

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder that affects up to 15% of the European and North American population, and is characterised by abdominal pain, bloating sensations, cramping, constipation, and diarrhoea. Main subtypes of IBS include constipation-predominant IBS (IBS-C), diarrhoea-predominant IBS (IBS-D), and mixed diarrhoea and constipation-associated IBS (IBS-M). The pathophysiology of IBS is still unclear, but important factors such as alterations in the brain-gut axis, bacterial overgrowth in the intestines, increased paracellular permeability, disruptions in the immune system, and accrued visceral sensitivity have been suggested. While many therapies are available to treat the symptoms associated with IBS, on a symptom-by-symptom basis, there are few effective treatments for IBS itself, including linaclotide, which was approved 2 years ago in Europe but only for IBS-C. Additional disease-modifying therapies to slow disease progression or achieve remission are needed as this represents a substantial unmet need. New emerging data on the pathophysiology of IBS are certainly promising; better knowledge of the underlying mechanisms will help refine the management of IBS, both in terms of diagnosis with the development of biomarkers, and in terms of therapeutic management with new pharmacological targets. Additional treatment options will be welcome given the variety of disease subtypes and presentations. The United European Gastroenterology (UEG) Week Congress, which was held in Vienna, Austria, 18th-22nd October 2014, was an excellent opportunity to share new findings on the pathophysiology and new clinical evidence and emerging therapies in the management of IBS. Selected abstracts received additional exposure through the "Posters in the Spotlight" session and the "Posters of Excellence" award; such abstracts will be developed in this review.

Keywords: Irritable bowel syndrome, immune system, pathophysiology, linaclotide, zonulin, permanent sacral nerve stimulation, Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols (FODMAP)-restricted diet, cyclic guanosine monophosphate (cGMP), colonic tone, somatisation.

INTRODUCTION

Irritable bowel syndrome (IBS) is a common gastrointestinal (GI) disorder that affects up to 15% of the European and North American population,[1-3] and that is characterised by abdominal pain, bloating sensations, cramping, constipation, and diarrhoea.[4] Main subtypes of IBS include constipation-predominant IBS (IBS-C), diarrhoea-predominant IBS (IBS-D), and mixed diarrhoea and constipation-associated IBS (IBS-M).

While the pathophysiology of IBS is still unclear, important factors such as alterations in the brain-gut axis, bacterial overgrowth in the intestines, increased paracellular permeability, disruptions in the immune system, and accrued visceral sensitivity have been suggested.[5-8] The United European Gastroenterology (UEG) Week Congress - held in Vienna, Austria, from 18th-22nd October 2014 - was an excellent opportunity to share new findings on the pathophysiology and new clinical evidence and emerging therapies in the

management of IBS. The UEG Week Congress gave additional exposure to select abstracts through the "Posters in the Spotlight" session, a new category introduced in 2014, aiming to promote hot topic research and providing in-depth scientific debates led by experts in the field; poster presenters were invited to present their work in sessions followed by an intensive discussion led by two moderators and experts in the field. The "Posters of Excellence" award honoured selected posters which were highlighted in a dedicated gallery and presented in 5-minute sessions. Such IBS-related abstracts selected by the organisation to highlight the currently most relevant topics in the field during the congress will be developed in this review.

NEW EVIDENCE ON THE PATHOPHYSIOLOGY OF IBS

The Guanylate Cyclase-C/Cyclic Guanosine Monophosphate (GMP) Pathway

Guanylate cyclase C (GC-C) is the target of linaclotide, which, as an agonist, activates its expression on intestinal epithelial cells triggering the release of cyclic GMP (cGMP) and thus accelerating the GI transit and inhibiting nociceptors in the colon.[9,10] The GC-C/cGMP pathway was further explored in 24 subjects - 10 healthy volunteers and 14 IBS patients - with the goal of comparing the expression of key components of this pathway on the colonic mucosa.[11] Seven IBS patients had IBS-M while seven others had IBS-C. Recto-sigmoid mucosal biopsies were conducted and mRNA expression of GC-C, guanylin and uroguanylin (endogenous GC-C agonists), and MRP4 and MRP5 (cGMP transporters). Immunohistochemistry was also performed to define the localisation of these components on cellular structures.

In IBS-M patients, both guanylin and uroguanylin expression were significantly reduced as compared to healthy controls ($p<0.05$ for both compounds). In IBS-C biopsies, MRP4 expression was significantly lower than in healthy controls ($p<0.001$). No statistically significant differences were observed for MRP5 or GC-C expression between all subgroups. Immunochemistry revealed that MRP4 was most present on the apical side of epithelial cells of the colon mucosa, while MRP5 was expressed on the basolateral side. These findings may help refine the pathophysiology of IBS and explain the discrepancy of symptoms among the disease subtypes, which warrant further investigation.

The Role of Intestinal Permeability and Zonulin Serum Levels

While the exact pathophysiological mechanisms of IBS are still unclear, increased intestinal permeability seems to be involved, particularly through zonulin (a pre-haptoglobin that is the human homologue of a toxin secreted by *Vibrio cholerae*), an endogenous modulator of intestinal permeability. Therefore, it would be a useful biomarker in diseases such as coeliac disease (CD), non-coeliac gluten sensitivity (NCGS), and IBS.

In a prospective study,[12] zonulin serum levels were evaluated by an enzyme-linked immunosorbent assay and spectrophotometrically in patients with NCGS (n=11) and IBS-D (n=9) and compared those of patients with CD (n=7; positive control) and healthy controls (n=7; negative control). Significant differences in zonulin serum levels were observed among the four groups. Serum zonulin levels were of 0.018±0.003 in IBS-D patients (healthy controls, 0.01±0.002; $p<0.05$). Overall, zonulin serum levels were positively correlated with serum anti-deamidated gliadin peptide and anti-transglutaminase antibodies, both involved in CD. These results indicate that zonulin, via its possible involvement in the pathophysiology of IBS, could be used as a diagnostic tool for IBS, but further clinical data are needed to clearly establish both its role and its potential as a biomarker.

The Role of the Immune System

Although IBS is considered a functional and neurological disorder, there is increased evidence of the role of an impaired immune system in IBS.[13] This impairment could manifest itself in the form a chronic low-grade immune activation impacting the visceral sensory nervous function and resulting in IBS symptoms. However, it is still unclear if these mechanisms are underlined by allergic or autoimmune pathways.

In a longitudinal, comparative study, Hughes et al.[13] investigated the immune activation in IBS in patients either presenting a flare or being symptom-free. Over 1 year, five IBS-D patients were assessed quarterly, by blood sampling, and also every single time the patient self-reported a symptom flare. Cell cultures were conducted and cytokine concentrations were reported after stimulation with lipopolysaccharides (LPS) or phorbol 12-myristate

13-acetate/ionomycin (PMA/I). At each visit, the patients completed questionnaires in the form of the IBS severity scale (IBSS).

IBSS scores were significantly higher during flare episodes, as compared with baseline values (quarterly assessments). Both innate (LPS stimulation: increased interferon gamma [IFN-γ], interleukin [IL]-2, IL-13, IL-21, granulocyte-macrophage colony-stimulating factor GM-CSF, and tumour necrosis factor alpha [TNF-α]) and adaptive (PMA/I: increased GM-CSF, IFN-γ, IL-10, IL-13, IL-17, IL-18, IL-21, IL-22, IL-23, IL-27, and TNF-α) arms of the immune response were altered in IBS-D patients during flare episodes. Further studies on wider cohorts comprising other IBS clusters are warranted to help define the role of the immune system in the pathophysiology of IBS, thus establishing potential biomarkers and new targets for novel therapies.

NEW EVIDENCE ON THE CLINICAL PRESENTATION OF IBS

Colonic Tone in IBS Patients

Bloating and visible abdominal distension are frequent manifestations of IBS, but these symptoms can be present in a variety of settings: in relation to food ingestion or not, or absent on waking and worsen during the day.[14] The colonic tone of 38 IBS patients (IBS-C 20, IBS-D 5, IBS-M 13) complaining of severe bloating and abdominal distension was evaluated in fasting and postprandial conditions.[15]

21 of the patients had a postprandial presentation and, in this subgroup, meal consumption was associated with a significant decrease of recto-sigmoid tone (mean postprandial recto-sigmoid volume modification was +26.6±4.4%). 17 patients had the symptoms regardless of food consumption and, in these, mean recto-sigmoid volume modification was -4.1±4.0%. The difference between both groups was significant (p=0.001), as also illustrated by the significant difference in abdominal girth (85.0±7.7 cm versus 83.4±7.2; p<0.01). These results highlight the possible pathophysiological involvement of decreasing intestinal tone in the postprandial period with respect to abdominal distension and bloating symptoms related to food intake.

Somatisation in IBS Patients and the General Population

While the associated prevalence of somatisation and IBS is well known, Palsson et al.[16] investigated the association between both aspects in the general population using data from a survey conducted in the US on 1,665 adults. This survey evaluated IBS and functional dyspepsia in the general population and included the Recent Physical Symptoms Inventory (RPSQ)[17] to assess somatisation, as well as the 12-Item Short Form Health Survey (SF-12) scale for quality of life (QoL), the ROME-III criteria[18] for IBS questionnaire and demographic and health history questions. Somatisation was calculated with the RPSQ answers as the number of different non-GI symptoms experienced more than once in the past month.

Among 1,277 validated forms, 7.1% of responders met Rome III criteria for IBS diagnosis while 4.5% of subjects met both IBS and functional dyspepsia criteria. Mean somatisation scores were 2-fold higher in IBS-positive subjects than in subjects not qualifying for IBS or functional dyspepsia (p<0.0001), regardless of ethnicity, gender, and age group, and even after subjects reporting physician diagnosis of any upper or lower GI disorders were removed from the analysis. Moreover, somatisation scores were consistent and significantly correlated (p<0.01) with key GI symptoms observed in IBS, such as pain anywhere in the abdomen (r=0.50), uncomfortable fullness after meals (r=0.49), pain/burning in the middle of the abdomen (r=0.41), and frequency of hard (r=0.38) and loose (r=0.38) stools.

In the IBS subpopulation, the most frequent symptoms were sleep difficulties (86%), muscle aches (82%), back pain (81%), headaches (79%), and muscle stiffness (66%), while IBS-positivity according to the Rome III criteria plus somatisation was negatively associated (p<0.01) with the SF-12 values (physical and mental composites, r=-0.51 and r=-0.35, respectively). Excess somatisation was observed in 42.9% of IBS cases. These findings highlight the link between IBS and somatisation, which is associated with impaired QoL.

NEW CLINICAL EVIDENCE ON THE MANAGEMENT OF IBS

Pharmacotherapy: Linaclotide

Linaclotide is a first-in-class, minimally absorbed, GC-C agonist that was approved by the FDA and

the EMA in 2012 for the treatment of IBS-C as it reduces abdominal pain and alleviates constipation in this subpopulation.[19] It was approved following two randomised, double-blind, placebo-controlled, multicentre Phase III studies, one of which evaluated once-daily 290 µg linaclotide for 12 weeks. After this period, patients receiving linaclotide were re-randomised to continue to receive linaclotide or placebo for 4 additional weeks.[20] Following the study completion and a randomised withdrawal period, patients could continue treatment within an open-label, long-term study.

In a post-hoc analysis, Díaz Gallo et al.[21] reported on the impact of linaclotide reintroduction on treatment satisfaction following a randomised period in which patients, after a 12-week linaclotide regimen, were reassigned either to linaclotide or placebo for 4 additional weeks. Subsequently, patients could receive linaclotide for up to 78 weeks (linaclotide-placebo-linaclotide and linaclotide-linaclotide-linaclotide arms in successive 12, 4, and 78-week periods). Patient-satisfaction was reported and used as an efficacy outcome, since patients were asked how satisfied they were with the ability of linaclotide to relieve their IBS-C symptoms on a 1-5 point scale.

During the 4-week randomised withdrawal period, patients assigned to the placebo group (who had previously received linaclotide) had significantly lower treatment satisfaction than patients who remained on active therapy (3.18 versus 3.46, respectively; $p<0.05$). In the placebo group, at the end of the withdrawal phase when linaclotide was reintroduced, treatment satisfaction returned to its initial values within a 2-week period (3.69 versus 3.70, respectively). Treatment satisfaction in both the linaclotide-placebo-linaclotide and linaclotide-linaclotide-linaclotide arms was sustained and increased through the end of the 78-week study (3.93 and 3.81, respectively). The most reported adverse event during the long-term study was diarrhoea, as reported in the Phase III trials. These results show that symptom control with linaclotide treatment can be re-established if treatment is re-introduced after a period of discontinuation.

Percutaneous Procedure: Permanent Sacral Nerve Stimulation (SNS)

SNS is a minimally invasive procedure that has been used in the last two decades to treat idiopathic faecal incontinence, but has recently been suggested as a useful procedure in diarrhoea-predominant IBS[22] or mixed-IBS.[23] Previously published results[24] suggested that SNS had no detectable effect on small intestinal transit patterns, as the median velocity of the magnetic pill through the small intestine in the fasting and the postprandial states was not significantly different between periods with and without SNS ($p=0.25$ and $p=0.14$, respectively).

At UEG Week 2014, Fassov et al.[25] presented their results on the medium-term for the same group of patients. 22 patients with severe diarrhoea-predominant or mixed IBS, who were eligible for the study, received an SNS implant. Main endpoints included change in the IBS-Symptom Severity Score (IBS-SSS) and in the IBS-specific QoL score. After a median follow-up of 42 months, the IBS-SSS was significantly lower than at baseline (26 versus 62, respectively; $p<0.0001$), regardless of the symptom cluster. The median IBS-specific QoL score was significantly improved (52 versus 134, respectively; $p=0.0001$), for all QoL domains. 82% of patients experienced persistent results, and 28% of those kept the stimulator for 5 years. While these findings warrant further investigation in larger cohorts and for longer treatment duration, in this study, the benefits of SNS therapy for selected patients with severe IBS were noteworthy and sustained at medium term.

Dietary Measures and Lifestyle Intervention: the FODMAP-Restricted Diet

At UEG Week 2014, new clinical evidence was presented on the Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols (FODMAP)-restricted diet. FODMAPs include fructose (fruits), lactose (dairy products), fructans (cereals, grains, and vegetables), galacto-oligosaccharides (vegetables), and polyols (used as sweeteners by the food industry).

The FODMAP-restricted diet was developed in Australia in the early 2000's by two researchers at Melbourne University who established the efficacy of this diet for the improvement of IBS-related symptoms.[26] The rationale behind the development of this restriction diet is that FODMAPs are fermentable carbohydrates which quickly affect the osmotic balance in the gut by increasing water resorption in the small bowel. FODMAPs processing by bacteria in the colon can also trigger intestinal lumen distension, bloating, and increased gas production, thus worsening the symptoms of functional GI disorders such as abdominal pain and

altered bowel movements. However, three previous clinical studies could not definitively establish the efficacy of the FODMAP diet in IBS, being one observational,[27] one retrospective,[28] and one with most patients unblinded.[29] In addition, many IBS patients autonomously reduce or eliminate gluten intake in their diet, reporting clinical benefit. It is not known to what extent the benefits of low-FODMAP diets are due to FODMAP per se or gluten reduction.

At UEG Week 2014, Piacentino et al.[30] presented the results of a double-blind, parallel group study to evaluate the effectiveness of a low-FODMAP diet and a low-FODMAP and gluten-free diet on abdominal bloating and pain in IBS patients; in addition, it evaluated patient compliance and satisfactory relief with the diets.

62 Rome III IBS outpatients (37 females; age range 21-67 years) were consecutively recruited. IBS patients, after registering their habitual diet for 2 weeks on a first daily diary card, followed the test or control diet for 4 weeks. During the last 2 weeks of the diet, they filled out a second daily diary card. There was comparable intensity of bloating and frequency of abdominal bloating and pain in the three groups pre-diet (p=0.217). However, a significant difference was observed in the same symptoms post-diet (p<0.001) with a greater improvement of IBS symptoms in the two test diet groups versus the control group, with a trend favouring the normal-gluten group versus the gluten-free group. Compliance was 90% in >85% of patients. IBS patients have considerable benefit by restricting FODMAPs in the diet. Gluten avoidance in addition to a FODMAP restricted diet does not offer any additional significant benefit.

At UEG Week 2014, van Megen et al.[31] presented the results from a 6-week intervention study. This study aimed to investigate the impact of this diet on patients with inflammatory bowel disease (IBD) who were in remission but with persistent IBS symptoms, as is often the case with IBD. 12 patients, of which 10 had ulcerative colitis and 2 had Crohn's disease, were included in the study. They presented C-reactive protein <5mg/L and faecal calprotectin <100 mg/kg, and fulfilled the ROME-III criteria for IBS. After determination of FODMAP intake for 4 days, a clinical dietician gave instructions to the patients on restricted intake. After 6 weeks, a second evaluation of FODMAP intake was conducted, as well as IBS symptoms, QoL, compliance, and colonic fermentation.

Mean compliance was 93%, with 73% of patients continuing the diet 1 month after study completion. Between the 0 and 6-week time points, FODMAP intake was significantly reduced (median 6.3 g to 1.5 g per day, p=0.0005). IBS symptoms, as assessed by the IBS-SSS, were significantly alleviated in the first 3 weeks to remain stable through week 6 (median scores of 265.0 and 67.6, respectively; p<0.0001), and this to the extent of achieving symptom remission (score <75) in 58% of patients. QoL, as evaluated by the 36-Item Short Form Health Survey (SF-36), was improved for the whole duration of the study, in terms of mental-related QoL (median score, 43.8 versus 53.3, respectively; p=0.039), physical-related QoL (mean score, 41.0 versus 47.1, respectively; p=0.05). The items most improved by the intervention were 'bodily pain' and 'vitality'.

The two studies indicated that FODMAP restriction diet alleviates symptoms in IBS patients and can alleviate symptoms and improve QoL in IBD patients experiencing IBS symptoms despite being in remission.

CONCLUSION

IBS-related posters, highlighted within the "Posters in the Spotlight" session and the "Posters of Excellence" award, presented new emerging and promising data on the pathophysiology of IBS, providing better knowledge of the underlying mechanisms to help refine the management of IBS, both in terms of diagnosis with the development of biomarkers and in terms of therapeutic management with new pharmacological targets. Additional treatment options will also be welcomed given the variety of disease subtypes and presentations.

Until now, therapy of IBS has been focused on the predominant symptom, either abdominal symptoms or bowel alterations, or a combination of therapies to deal with both abdominal and bowel disturbances. Many therapies are available to treat the symptoms associated with IBS on a symptom-by-symptom basis, and a FODMAP-restricted diet can be now added to the therapeutic armamentarium to deal with abdominal pain and bloating. Nevertheless, linaclotide (indicated in IBS-C, regardless of gender) and lubiprostone (only approved in the USA for treatment of IBS-C in women aged 18 years and older) are the only agents that demonstrated their efficacy for both

abdominal symptoms and constipation in IBS-C patients, and, as highlighted by the American College of Gastroenterology, are also the only two compounds which are strongly recommended for IBS-C due to high and moderate quality of evidence, respectively.[1] Additional disease-modifying therapies to slow disease progression or achieve remission are needed as this represents a substantial unmet need.

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A PROKINETIC AGENT WITH A DUAL EFFECT – ITOPRIDE – IN THE TREATMENT OF DYSMOTILITY

***Petr Dite, Martin Rydlo, Milan Dockal, Arnost Martinek**

Academic Centre of Gastroenterology, Department of Internal Medicine of the University Hospital and the Faculty of Medicine of the University of Ostrava, Ostrava, Czech Republic
**Correspondence to pdite.epc@gmail.com*

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ABSTRACT

A wide range of dyspeptic symptoms in clinical practice reflect the high prevalence of functional disorders of the gastrointestinal (GI) tract. Prokinetic agents are the current mainstay in the therapy of functional dyspepsia. One of these drugs is itopride. We evaluated therapeutic efficacy of itopride according to the literature review. The therapeutic potential of itopride is connected with a dual effect: influencing of enzyme acetylcholinesterase activity and blocking dopamine D2 receptors. After the itopride administration, the contractility of smooth muscle in the upper GI tract increases. Itopride is a drug with rapid absorption from the small bowel; its peak serum concentration occurs 35 minutes after oral administration. Itopride does not pass the blood-brain barrier and does not affect the heart rate by influencing the QT segment. Itopride is a safe prokinetic agent with positive influence on the symptoms of functional dyspepsia such as postprandial fullness, bloating, and gastric emptying. Itopride could also be used for the therapy of the mild form of gastro-oesophageal reflux.

Keywords: Gastro-oesophageal reflux, gastric motility, gastroduodenal coordination, functional dyspepsia, prokinetic agents, itopride, dopamine D2 receptor, acetylcholinesterase.

INTRODUCTION

Patients with impaired gastric motility rank among the most examined groups of patients. The physiological gastric motor function includes the ability of the stomach to act as a reservoir of food during food intake, gastric emptying, and coordination of interdigestive motility.[1] Functional dyspepsia and gastroparesis are the main syndromes associated with gastric motor dysfunction. Failure of gastric emptying was demonstrated in 30% of patients with functional dyspepsia.[2] The concept of functional dyspepsia is the relationship between psychosocial and physiological factors, functional gastrointestinal (GI) symptoms, and clinical outcome. Early in life, genetic as well as environmental factors may affect psychosocial development and the development of gut dysfunction. A crucial role is played by the brain-gut axis. Persons with high life-stress, coexisting psychosocial comorbidities, or maladaptive coping could develop a syndrome, e.g. postinfectious dyspepsia. There is no doubt that genetics, environmental factors, and psychosocial factors significantly influence physiological functions of the GI tract (motility, sensation, inflammation, and bacterial flora).

Therapy aimed at correction of the symptoms of functional dyspepsia and gastroparesis is medically based on the effect of drugs referred to as prokinetic agents. GI prokinetic agents stimulate the contraction of the smooth muscle of the gastric wall, thereby affecting gastric emptying. Prokinetic agents represent a heterogeneous group of drugs that realise their effect through an agonistic effect on 5-HT receptors, dopamine D2 receptors (DD2Rs), or motilin and ghrelin receptors. This group also includes a prokinetic agent of a new generation, having the dual effect on motility - itopride.

CHARACTERISTICS OF ITOPRIDE

Itopride is a prokinetic agent with a slight antiemetic effect, whose main effect is influencing oesophageal peristalsis, stimulating gastric motility, and stimulating gastric emptying, with a positive influence on gastroduodenal coordination. Itopride has a dual effect on the motility of the GI tract. A stimulatory effect on the motility of the GI tract is mediated both by DD2R antagonist properties and by inhibiting the degradation of acetylcholine.[3] Dopamine is a substance with an inhibitory effect on the motility of the GI tract.[4] D2 receptors are located only in the upper digestive tract, particularly in the oesophagus and stomach, where the effect of itopride can be exhibited.

The second mechanism of itopride activity is inhibition of acetylcholinesterase. Acetylcholinesterase inhibition increases the amount of acetylcholine at nerve synapses. The result is an increase in the motility of the oesophagus and stomach, including emptying.[5] Dependence on the administered dose of the substance has been proven; this observation is important, when in the experiment the overall effect of itopride, i.e. influencing D2 receptors and inhibition of acetylcholinesterase, was demonstrable throughout the entire alimentary tract.[3]

The effect of itopride is an increase in acetylcholine concentration, which promotes gastric motility, increases the lower oesophageal sphincter (LOS) pressure, accelerates gastric emptying, and improves gastroduodenal coordination. The significant itopride pharmacokinetic properties include its very rapid absorption when administered orally; the maximum plasma has been shown as early as 35 minutes after administration.[6] Itopride is metabolised in the liver by the enzyme Flavin, containing monooxygenase, and its excretion from the body occurs primarily through the kidneys, where part of itopride is eliminated, unchanged, in the urine, mainly in the form of its metabolite.[6]

Itopride does not cross the blood-brain barrier; it has no relevant drug-drug interactions, probably because it is not metabolised in the liver by the cytochrome P450 activity. Itopride is considered a safe drug; in the Holtmann et al.[7] study, the most frequent adverse symptoms were dull abdominal pain, diarrhoea, or vice versa constipation, and nausea. Their frequency, however, did not differ from the group treated with a placebo.[7] Prolactinaemia, galactorrhoea, or leukopaenia are rarely present. Because itopride is excreted in breast milk, the drug is not recommended for pregnant women and children.

Indications

Generally, itopride is indicated in patients with symptoms of impaired oesophageal motility, impaired gastric emptying, including disorders of gastric emptying in diabetic patients, and those with functional dyspepsia and gastro-oesophageal reflux (GOR).

CLINICAL RESULTS

Itopride was developed in Japan; the first clinical studies in international journals were published in India. The first Indian studies evaluated the changes of initial subjective symptoms in people with dyspepsia in whom endoscopic examination did not lead to conclusive diagnosis of gastritis or peptic ulcer disease. In >70% of subjects, a significantly positive effect on symptoms was described after 14-day itopride medication at a dose of 50 mg, thrice a day (TID).[8] The second Indian study compared the influence of therapy with itopride or domperidone on subjective symptoms in patients with functional dyspepsia. The effect of therapy was higher in the group treated with itopride.[9] A similar conclusion was reached by the third study, comparing itopride with mosapride, which demonstrated better effect in the itopride group. In all studies, itopride was a safe drug.[10]

Itopride in the Treatment of Functional Dyspepsia

In 2006, results of a prospective, randomised, and multicentric study evaluating the results of itopride therapy in a representative sample of 523 persons, meeting the Rome II criteria,[7] were published. The studied subjects were randomised into three groups with a different dosing schedule. The first group received 50 mg of itopride TID, the second group 100 mg of itopride TID, and the third group was administered 200 mg of itopride TID. The study lasted for 8 weeks and the evaluated factors were the effect of the therapy, changes in symptoms of dyspepsia according to a standardised questionnaire and a five-point scale (some changes were evaluated, such as abdominal pain, the presence of nausea, or early satiety feeling), and the overall effect of the therapy by the patient himself/herself was also assessed.

All three doses of itopride demonstrated significantly better symptomatic relief and improvement when compared with the placebo. Overall analysis revealed that itopride was significantly superior to placebo, with the greatest symptom-score improvement in the 100 and 200 mg groups, when the statistical significance of difference between the placebo and dosage of 200 mg TID was at p<0.001. The quality of life (QoL) of the treated individuals, evaluated at the end of the study, was also better than in the placebo group. The Nepean Dyspepsia Index QoL score improved by a mean of 13.2±19.4 with placebo, and by 18.0± 21.9 with itopride. The dosage used within the study with two groups exceeded the recommended dosage for clinical practice (50 mg TID). It is therefore interesting that the percentage of side-effects in all three treated groups did not differ significantly, and it was not even different compared to the placebo. The most common side-effects were abdominal pain, diarrhoea, constipation, and nausea. Prolactin levels were higher, mainly in groups with higher drug dosage; however, no relevant clinical symptoms of prolactinaemia have been recorded.

Soji[11] investigated the effect and safety of itopride in a randomised and placebo-controlled study, in a group of 67 persons with functional dyspepsia. Participants met the Rome II diagnostic criteria; the subject age ranged from 18-60 years and a predominance of symptoms of early satiety, post-prandial fullness, and bloating were selected. The subjects were randomised; one group was treated with itopride at a dose of 50 mg TID, the other with a placebo. After 4 weeks of therapy, the symptom score of people treated with itopride was positively influenced in contrast to the placebo-treated group, statistically significant at p=0.0004 (before the start of itopride or placebo therapy, the symptom score in both groups was identical). In this study, in the group with strictly set selection criteria, itopride proved to be an extremely effective medicine with minimal side-effects (abdominal discomfort in two persons). None of the treated individuals showed abnormal ECG changes in terms of prolongation of the QT segment, which is a known limitation of functional dyspepsia cisapride therapy.

In 2011 Sun et al.[12] published the data from a prospective, multicentre, post-marketing observational study. 576 patients with functional dyspepsia were enrolled. Patients were prescribed itopride 50 mg TID before meals for 4 weeks. The treatment response rates after 1 week of therapy in patients with ROMA I, ROMA II, and ROMA III criteria for functional dyspepsia were 33.68%, 34.71%, and 35.50% respectively, and 72.82%, 73.54%, and 75.15% after 4 weeks. Itopride was well tolerated; there were no serious adverse reactions.

In 2012, Huang et al.[13] published a meta-analytic study evaluating the effect of itopride in the treatment of functional dyspepsia. It evaluated the effect of itopride, domperidone, mosapride, and placebo in subjects with a diagnosis of functional dyspepsia. The results of 9 randomised, placebo-controlled trials involving a total of 2,620 treated individuals were evaluated. 1,372 patients were treated with itopride at a dose of 50 mg TID each, and 1,248 persons constituting the control group were taking other drugs, i.e. domperidone, mosapride, or a placebo. The effect of therapy in the group treated with itopride was significantly higher when compared with the control group (p=0.006 placebo, p=0.02 persons treated with domperidone, and p=0.04 in subjects treated with mosapride) for global patient assessment, postprandial fullness, and early satiety. The earliness of therapy side-effects was similar for all administered drugs; statistically, it did not significantly differ. From this study it can be clearly concluded that itopride is an effective and safe remedy for the symptoms of functional dyspepsia, especially the syndrome of early satiety and postprandial fullness.

Itopride and Gastric Emptying

In experimental animal studies, itopride stimulates the motility of the stomach, duodenum, small intestine, and colon.[14,15] Choung et al.[16] in a double-blind, randomised, placebo-controlled trial of itopride on gastric motor activity and sensory function in healthy volunteers, monitored 16 people with itopride medication at a dose of 100 mg TID, 16 people with medication at a dose of 200 mg TID of itopride, and 15 persons with a placebo.[16] In healthy volunteers, the authors - contrary to others[17] - did not show the effect of itopride on gastric emptying, but they believe that itopride may have the effect due to increasing muscle contractility of the proximal and distal stomach after eating. An interesting finding is the significant acceleration of small bowel transit time after administration of 200 mg of itopride when compared with the placebo. The authors did not demonstrate that itopride in large doses significantly affects the stomach and gastric sensory function in healthy people. It can, however, be considered that the

effect in healthy persons may be different from that in patients with functional dyspepsia.

An interesting observation is published by Lim et al.,[18] who evaluated the effect of prokinetics, including itopride, on electrogastrography parameters, according to symptomatic changes in patients with functional dyspepsia. He concluded that prokinetic drugs could improve the symptoms of functional dyspepsia by regulating gastric myoelectrical activity. This finding is important only because gastric dysrhythmias are described in 31-69% of patients with functional dyspepsia.[19] Simanenkov et al.[20] demonstrated that itopride therapy at a dose of 50 mg TID led, by affecting gastric function, to significant suppression of the initial symptom, which was epigastric pain syndrome.

In individuals with concurrent diabetes mellitus Type 1 or 2, 30-50% of patients have delayed gastric emptying. It has been shown[21] that, compared to a placebo, itopride effect in those persons leads to a significant acceleration of discharging both liquid and solid food from the stomach. The effect of itopride does not contribute to changes in glucose levels during medication. However, it is beyond any doubt that failure of gastric emptying is closely associated with glycaemic control, which in itself significantly affects gastric evacuation.[22,23]

GOR

Scarpellini et al.[24] examined itopride effect on the function of the LOS during fasting and after eating in a group of 12 volunteers. After 3-day itopride premedication at a dose of 50 mg (BID), 100 mg (BID), or administering a placebo, oesophageal manometry was carried out. The drugs were administered 30 minutes before the application of a standardised diet. Resting pressure of LOS, swallow-induced relaxations, or duration of peristaltic contractions were not altered by both doses of itopride. Itopride pre-treatment inhibited the meal-induced rise of transient LOS relaxations. Itopride inhibited the transient LOS relaxation without a significant influence on oesophageal peristaltic function or LOS pressure. Kim et al.[25] studied the effect of itopride in patients with GOR. Patients with GOR disease were treated with 150 mg and 300 mg of itopride, thrice a day. Prior to the study, which lasted for 8 weeks, and after it finished, a 24-hour pH monitoring was carried out. The total symptom score was significantly improved after treatment with both doses of itopride used, while a greater effect was observed in the group receiving 300 mg itopride daily, using the DeMeester score, and the total pH time of 4.0. The Korean study[26] investigated whether the addition of itopride to proton pump inhibitors affects the healing effect in patients with a laryngeal form of reflux. The authors have not demonstrated that dual therapy yields better results than therapy with proton pump inhibitors only.

Itoprid and Colonic Function

In an experimental study, when the effect of itopride was evaluated in the excised distal ileum from a guinea pig, acceleration of peristaltic velocity was at higher dosage, whereas neostigmine accelerated it only with a lower dosage. Dopamine-decelerated velocity was recovered by itopride infusion. Itopride has prokinetic effects on both the ileum and colon via inhibitory effects on acetylcholinesterase and antagonistic effects on dopamine receptor.[4]

SUMMARY

Dyspepsia is a term used for a set of different symptoms, including epigastric discomfort, bloating, nausea, anorexia, postprandial fullness, belching, heartburn, and regurgitation. The fundamental requirement is to distinguish whether these symptoms are due to organic changes of the upper digestive tract, or whether it is a functional dyspepsia, present in about 60% of patients with dyspeptic symptoms. A wide range of dyspeptic symptoms reflect the high prevalence of functional disorders of the GI tract.[27,28] The drugs that are indicated in the treatment of functional dyspepsia symptoms include prokinetic agents. Itopride ranks among the prominent prokinetic agents.

Itopride is indicated in all patients with functional dyspepsia, in patients with dyspeptic symptoms, when these symptoms are present in the absence of structural or biochemical abnormalities and detected by routine diagnostic methods. Functional dyspepsia is defined as the presence of symptoms thought to originate in the GI region in the absence of organic, systemic, and metabolic disease that is likely to explain the symptoms.[28] The therapeutic effect of itopride is connected with its dual effect, consisting in influencing the levels of the enzyme acetylcholinesterase, which consequently affects the level of acetylcholine. This results in increasing the contractility of the smooth muscle of the intestinal wall through a D3 receptor. At the same time, itopride affects dopaminergic innervation of the smooth muscle of the upper GI tract by blocking

DD2Rs; itopride is extremely rapidly absorbed, and its peak serum concentration occurs 35 minutes after oral administration.[29]

In a meta-analytic study evaluating the effect of itopride in functional dyspepsia, published by Huang et al.[13] authors collected 328 articles, 319 of them were excluded, and 9 randomised controlled trial articles were included. Included studies contained a total of 2,620 patients; 1,327 were treated with itopride and 1,248 received placebo. Efficacy of itopride with respect to postprandial fullness in patients with functional dyspepsia was significantly demonstrated (p=0.02). This effect was more significant than the effect of domperidone. Itopride also significantly improved symptoms of early satiation in patients with functional dyspepsia (p=0.04). In placebo-controlled studies evaluating LDQ-scores (Leeds Dyspepsia Questionnaire) in patients with functional dyspepsia, itopride improved the LDQ scores more significantly than placebo (p<0.001). Itopride and domperidone had similar efficacy on epigastric discomfort of functional dyspepsia (p=0.98).

Itopride is a safe drug and, unlike (for example) metoclopramide, it does not pass the blood-brain barrier; additionally, unlike cisapride, it does not affect the heart rate by prolonging QT segment.[30] According to these results there is no doubt that itopride therapy positively influences the symptoms of functional dyspepsia, especially postprandial fullness, bloating, and LDQ. Itopride in clinical studies positively affected conditions with prolonged gastric emptying, including disorders of gastric emptying in diabetic patients. In the mildform of GOR, itopride was proven as a potential part of the treatment armentaria, where a fundamental role is played by the blockades of the proton pump.

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RISKS OF USING BEDSIDE TESTS TO VERIFY NASOGASTRIC TUBE POSITION IN ADULT PATIENTS

***Melody Ni,[1] Oliver Priest,[1] Lawrence D. Phillips,[2] George B. Hanna[1]**

1. Department of Surgery and Cancer, St Mary's Hospital, Imperial College London, London, UK
2. Department of Management, London School of Economics and Political Science, London, UK
**Correspondence to z.ni@imperial.ac.uk*

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ABSTRACT

Nasogastric (NG) tubes are commonly used for enteral feeding. Complications of feeding tube misplacement include malnutrition, pulmonary aspiration, and even death. We built a Bayesian network (BN) to analyse the risks associated with available bedside tests to verify tube position. Evidence on test validity (sensitivity and specificity) was retrieved from a systematic review. Likelihood ratios were used to select the best tests for detecting tubes misplaced in the lung or oesophagus. Five bedside tests were analysed including magnetic guidance, aspirate pH, auscultation, aspirate appearance, and capnography/colourimetry. Among these, auscultation and appearance are non-diagnostic towards lung or oesophagus placements. Capnography/colourimetry can confirm but cannot rule out lung placement. Magnetic guidance can rule out both lung and oesophageal placement. However, as a relatively new technology, further validation studies are needed. The pH test with a cut-off at 5.5 or lower can rule out lung intubation. Lowering the cut-off to 4 not only minimises oesophageal intubation but also provides extra safety as the sensitivity of pH measurement is reduced by feeding, antacid medication, or the use of less accurate pH paper. BN is an effective tool for representing and analysing multi-layered uncertainties in test validity and reliability for the verification of NG tube position. Aspirate pH with a cut-off of 4 is the safest bedside method to minimise lung and oesophageal misplacement.

Keywords: Decision analysis, Bayesian networks, nasogastric tube, patient safety.

INTRODUCTION

At least one million nasogastric (NG) feeding tubes are purchased by the National Health Service in England each year. Complications of feeding tube misplacement include malnutrition, pulmonary aspiration, and even death. For blind insertion, the rate of respiratory placement is typically 1-3%. Inadvertent tube placement in the oesophagus was observed in 19 out of 100 blind NG tube insertions.[1] Reported rates of tube misplacement on insertion and tube migration after correct initial placement vary between 1.3% and 50% in adults.[2]

There is a distinct lack of consensus as to the optimum method of checking the feeding tube position. In response to several deaths directly related to NG tube misplacement, the National Patient Safety Agency (NPSA) in England issued safety alerts in February 2005 to describe correct procedures for checking the position of feeding tubes.[3,4] However, additional cases of death due to NG tube misplacement have been reported since the circulation of these alerts. Possible reasons include the use of inappropriate checking procedures or the misinterpretation of radiographs by clinicians. Also documented are the life-threatening complications from enteral formulations or medications entering the lung through a misplaced NG tube, i.e. 'aspiration-by-proxy', that did not result in patient harm.[5] The most recent safety guideline forbids the use of auscultation ('the whoosh test'), while recommending testing of the tube aspirate pH

(cut-off 5.5) and the use of chest radiographs whenever necessary.[6]

The task to correctly position a blindly inserted NG tube is challenging because none of the bedside procedures can provide definitive verification of tube position. Even the current gold standard of a chest radiograph is prone to misinterpretation. We were commissioned by NPSA to review the safety of using bedside methods to verify NG tube position with an emphasis on confirming initial tube placements prior to feeding.

METHODS

A Bayesian network (BN) was constructed to analyse risks in safe feeding. BNs are graphical tools for reasoning with uncertainties.[7-9] They can be viewed as a special knowledge network that captures one's beliefs in a risky decision. Each node (circle) represents an uncertain event; each arrow (or edge) represents dependence between two events, and the lack of arrow indicates conditional independence. The structure of a BN reflects how we think different events relate to each other. The numerical part of a BN in the form of conditional probabilities reflects the strength of such dependence. In the case of NG tube positioning, the tube site is the shared parent node of different bedside tests. Arrows pointing out from tube site and into the bedside tests indicate our belief that the outcome of these tests depend, among other things, on the location of the feeding tube which could be lung, intestine, stomach, or oesophagus. No arrows, however, link different tests together because we believe that the outcome of one test (its findings) does not depend on those of another test (conditional independence). For aspirate pH, feeding and medication history of a patient were modelled as additional parents of the pH test; pH paper was modelled as a child of pH meter (which is a child of tube site). This allows us to examine test results from various combinations of feeding and medication conditions, as well as to test using a less reliable measurement of pH.

We capture the risk of tube misplacement during initial insertion (i.e. before checking) in the prior distribution of the tube sites. Test validity (i.e. sensitivity and specificity) was incorporated as conditional probability of a finding in each tube site. Once a finding has been entered into the BN, the prior distribution will be updated according to the Bayes' rule. The result is the posterior distribution of the tube sites that reflects one's revised belief about the location of the NG tube in light of the finding. We built the BN in software Netica®.

Information on test validity was retrieved from a systematic review in which chest X-rays served as the gold-standard. Multiple sources of information on the same test were combined by a simple weighted average, based on sample size. Missing information was dealt with by assuming a flat distribution where all the findings were assumed to be equally likely. For aspirate pH, raw data were kindly provided by the author (Prof Norma Metheny).[10-16] This enabled a detailed study of the influence of antacid medication and feeding status of a patient, as well as measurement methods such as Baxter paper versus pH meter. We generally assume that the tube had 20%, 50%, 20%, and 10% probabilities of being inserted into the lung, stomach, oesophagus, and small bowel, respectively.[1,2] We also tested scenarios of low initial risks (prior probabilities of lung/stomach/oesophagus/small bowel =10%/80%/10%/0%) and high initial risks (prior =30%/35%/25%/10%) where tube misplacements were respectively 30% and 65% of the time, compared to 50% of the time, as widely assumed. The likelihood of safe feeding varies with tube site. The consequences of feeding into a misplaced tube in the lung are the most severe, followed by oesophagus, and small bowel. We used likelihood ratios (LRs) to prioritise safety needs. LR_1, LR_2, and LR_3 measured the capacity of a test to detect tubes in the lung, oesophagus, and small bowel in contrast to the stomach (the correct tube site).(*)

$LR_1 = p(\text{finding}|\text{not lung}) / p(\text{finding}|\text{lung})$

$LR_2 = p(\text{finding}|\text{stomach}) / p(\text{finding}|\text{oesophagus})$

$LR_3 = p(\text{finding}|\text{stomach}) / p(\text{finding}|\text{small bowel})$

Two types of findings are worth noting. Infinite LR_1, LR_2, and LR_3 indicate that lung, oesophagus, and small bowel misplacements are ruled out, in which case feeding can safely start. An example is the finding of a stomach tube using correctly interpreted chest X-rays, the current gold-standard. Secondly, zero LRs would confirm the lack of safety as the tube is in the lung (LR_1) or outside the stomach (LR_2 and LR_3). This happens when a lung tube is found by correctly interpreted chest X-rays. Note that under the assumption of conditional independence, the utility of several tests, when used

together to verify tube site, was simply the product of their respective LRs.

RESULTS

Aspirate pH,[10-13,16] appearance,[11] auscultation,[10,17] capnography/colourimetry,[11] and magnetic guidance[18] emerged from our literature review as existing or potential bedside tests for locating blindly inserted NG tubes. The BN is shown in Figure 1. Contained within each bedside test are its findings; next to each finding is the joint (average) probability of observing the finding given the test validity (Table 1(**)) and the prior probabilities that the tube is inserted into the lung, stomach, oesophagus, and small bowel, respectively (i.e. 20%, 50%, 20%, and 10%; Figure 1). Note that we included the discredited auscultation test in our analysis, for two reasons: firstly to provide a check on the validity of model predictions and secondly, to analyse its potential when used in combination with other tests. For the aspirate pH, we chose 4.0, 5.0, 5.5, and 6.0 as the cut-offs (findings). Table 1 presents the combined (averaged) sensitivity of each finding of each test. The pH from oesophageal intubation was extrapolated from studies on reflux patients, which together demonstrate that the median percentage time with oesophageal pH measured <4.0, is between 0.5-3.1% of recorded 24-hour periods in healthy individuals;[19-24] sensitivity of the pH test above 4 was assumed to be evenly distributed. A lack of high-quality evidence for auscultation test also led us to assume that the loudest sound was equally likely to be heard in epigastrium, left upper quadrant (LUQ), and right upper quadrant (33% in each case) through lung tubes.

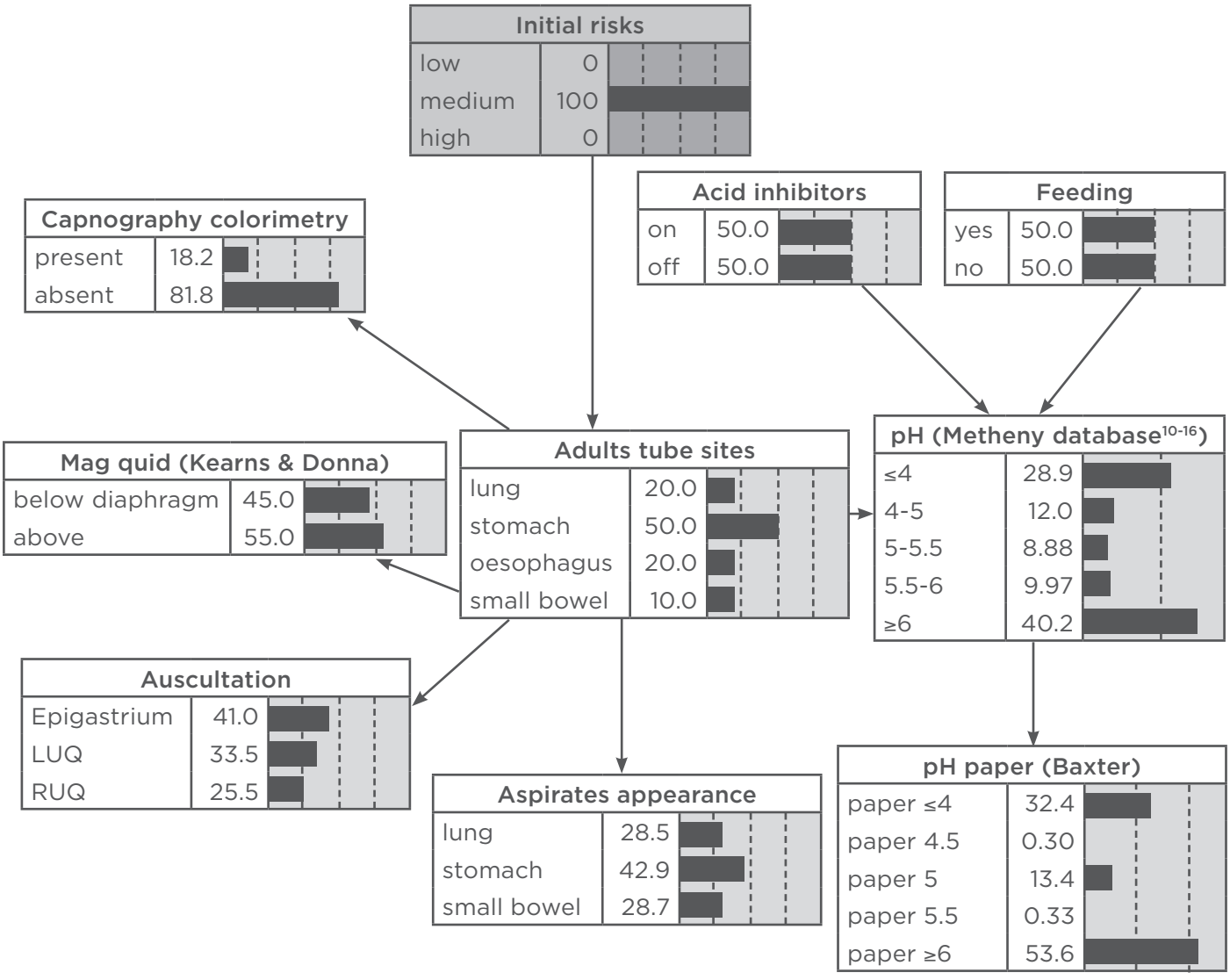

Figure 1: The Bayesian Network model for the safe verification of nasogastric tubes.
LUQ/RUQ: left/right upper quadrant.

Table 1: Sensitivity of the bedside tests in positioning blindly inserted NG tubes.

Test	Findings	Lung	Stomach	Oesophagus	Small Bowel
pH Meter	≤4	0.00	54.60%	5.00%	6.26%
	≤5	0.00	67.80%	30.00%	10.13%
	≤5.5	0.00	75.23%	55.00%	11.80%
	<6	0.36%	84.51%	80.00%	14.38%
	≥6	99.60%	15.50%	20.00%	85.60%
Auscultation	Epigastrium	33.30%	29.20%	62.00%	73.60%
	LUQ	33.30%	41.60%	19.00%	22.40%
	RUQ	33.30%	29.20%	19.00%	4.00%
Appearance	Lung	46.10%	21.20%	33.30%	20.00%
	Stomach	26.90%	57.60%	33.30%	20.00%
	Small bowel	26.90%	21.20%	33.30%	60.00%
Capnography	CO_2 present	89.30%	0.40%	0.40%	0.40%
	CO_2 absent	10.70%	99.60%	99.60%	99.60%
Magnetic Guidance	Below diaphragm	0.00	75.00%	0.00	75.00%
	Above diaphragm	100.00%	25.00%	100.00%	25.00%

NG: nasogastric; LUQ/RUQ: left/right upper quadrant.

Table 2: The effectiveness of the bedside tests to rule out lung and oesophagus (infinite LRs).

Test	Findings	LR_1	LR_2	LR_3
pH	≤4	Infinite	10.92	8.72
	≤5	Infinite	2.26	6.69
	≤5.5	Infinite	1.37	6.38
	<6	207.22	1.06	5.88
	≥6	0.26	1.29	0.18
Auscultation	epigastrium	1.29	0.47	0.40
	LUQ	1.01	2.19	1.86
	RUQ	0.71	1.54	7.30
Appearance	lung	0.52	0.64	1.06
	stomach	1.74	1.73	2.88
	small bowel	1.08	0.64	0.35
Capnography	CO_2 present	0.004	1.00	1.00
	CO_2 absent	9.31	1.00	1.00
Magnetic guidance	below diaphragm	Infinite	Infinite	1.00
	above diaphragm	0.44	0.25	1.00

LRs: likelihood ratios; LR_1: p(finding|not lung)/p(finding|lung); LR_2: p(finding|stomach)/p(finding|oesophagus); LR_3: p(finding|stomach)/p(finding|small bowel); LUQ/RUQ: left/right upper quadrant.

Table 2[**] presents the LRs based on test validity (Table 1) and the prior. A quick scan of Table 2 shows that the best tests to detect lung intubation, as indicated by an infinite LR_1, are pH (5.5 or lower) or magnetic guidance (below diaphragm), and the best tests to detect oesophageal intubation, as indicated by an infinite LR_2, are magnetic guidance (below diaphragm), followed by aspirate pH with a cut-off at 4. The latter can reduce the chance of oesophagus placement relative to stomach placement by nearly 10-fold (LR_2=10.92). In contrast, the chance of oesophagus placement would barely change when a pH of 5.5 or less is observed (LR_2=1.37).

Using the BN model in Netica, a pH of 5.5 or less would predict the probabilities of lung, stomach, oesophagus, and small bowel placements are 0%, 75.5%, 22.1%, and 2.37% respectively, in contrast to the initial 20%, 50%, 20%, and 10%. A pH of 4.0 or less would predict the probabilities of lung, stomach, oesophagus, and small bowel placements are 0%, 94.4%, 3.46%, and 2.16%, respectively. That is, a pH at 4 or less reduces the risk of oesophageal intubation from 20% to 3.46%, i.e. from fairly uncertain to 'beyond reasonable doubt'.

Auscultation and appearance are not useful on their own as their LRs clustered around 1. The only finding useful in terms of lung and oesophagus intubations is the auscultation test which found the loudest sound heard in the LUQ (LR_2=2.19). This would halve the chance of oesophageal placement (from 20% to 11.3%) relative to stomach placement (from 50-62.1%). Using capnography or colourimetry, detecting CO_2 would increase the chance of lung tubes from 20-98% (LR_1=0.004). However, the absence of CO_2 cannot be taken as definitive evidence that the tube is outside the lung (LR_1 =9.31), and the revised belief of lung placement is 2.62%.

Feeding, Antacid Medication, and Measurement Technique Effects on pH Test

Recent feeding, administration of antacid therapy, or using pH paper instead of meter to measure pH, all reduce sensitivity of the pH test. Given a pH of 5.5 or less, receiving antacids would increase the chance of oesophagus placement from 22.1-23.6%, though feeding had little impact. Given the finding of a pH of 4.0 or less, receiving antacids would increase the chance of oesophagus placement from 3.46-4.05% and further to 4.20% if the patient has recently been fed. If Baxter paper is used instead of pH, the reading of 4 or less would predict the probabilities of stomach, oesophagus, and small bowel placements to be 89.2%, 8.49%, and 2.30%, whereas a reading of 5.5 or less would predict the probabilities of lung, stomach, oesophagus, and small bowel placements to be 0.024%, 78%, 19.6%, and 2.41%.

Impact of Low or High Initial Risks on pH

If a pH of 4 or less was observed, the predicted probabilities of lung, stomach, oesophagus, and small bowel placements were respectively 0%, 98.9%, 1.13%; 0% under low level of initial risks; and 0%, 91.1%, 5.96%, and 2.98% under high level of initial risks. If a pH of 5.5 or less was observed, the chances of lung, stomach, oesophagus, and small bowel placements were 0%, 91.6%, 8.37%, and 0% likely under low level of initial risks and 0%, 63.8%, 33.3%, and 2.86% likely under high level of initial risks.

Assume a worst case scenario where the initial insertions have a high risk of misplacements and the verification is done by Baxter paper instead of pH meter. A finding of a pH of 5.5 or less would predict lung, oesophagus, and small bowel misplacements to be 0%, 54.6%, and 2.03% respectively, whereas a pH of 4 or less would predict the probabilities of lung, oesophagus, and small bowel misplacements to be 0%, 8.49%, and 2.30%, respectively. That is, if a patient is fed after a pH of 5.5 or less is observed in the worst case scenario, then half of the time the feeding would be in the oesophagus instead of the stomach.

DISCUSSION

Five bedside tests were investigated, i.e. magnetic guidance, aspirate pH (with cut-offs 4, 5, 5.5, and 6), auscultation, aspirate appearance, and capnography/colourimetry. Consistent with the existing literature and the recommendation of NPSA, neither auscultation nor aspirate appearance can be recommended for use on their own to detect tube misplacements in the lung or oesophagus. It is worth noting that if capnography/colourimetry is used, the absence of CO_2 cannot be taken as evidence for safe feeding (outside the lung) because such findings are observed in 10.7% of the lung placements (Table 1). The safest tests are magnetic guidance and pH of tube aspirate. Magnetic guidance can rule out lung or oesophageal placement – the two most hazardous potential tube

sites, whereas a pH test with cut-offs at 5.5 or lower can rule out lung misplacements. Further lowering the cut-off to 4 or less would minimise oesophagus misplacements. Magnetic guidance is a relatively new technology and has a relatively small, though growing, evidence base (n=243).

Magnetic guidance has been studied in adults and children, particularly in the context of post-pyloric feeding with retrospective studies.[25-27] More recent prospective studies indicate encouraging accuracy of the technique[28] but there are additional costs of technical equipment and devices required for every tube placement[29] and the process does not eliminate the risk of adverse soft tissue injury.[30] Further validation studies are needed.

The pH test of tube aspirates is widely used, well-studied, and has an established evidence base (nearly 800 cases in our database). Current practice also recommends the use of aspirate pH, though with a cut-off of 5.5. Our analysis shows lowering the pH cut-off from 5.5 to 4.0 can enhance safety in oesophageal intubations. Furthermore, the use of Baxter paper, feeding, medication history of a patient, and potential variations in the risks in the initial insertions of the tube, means a lower pH would provide an extra layer of safety for reducing oesophageal feeding. Lowering the pH threshold would result in more patients with tubes correctly placed in the stomach to be sent for X-rays (unnecessary X-rays). It is therefore a trade-off that needs careful assessment: minimising placement errors (mainly in the oesophagus) versus minimising unnecessary X-rays. Consider three strategies in Table 3, i.e. X-ray all patients, X-ray only patients with pH higher than 5.5, or X-ray only patients with pH higher than 4. Under the assumption of 50% initial insertion errors, adopting a pH with a cut-off of 4 would reduce placement errors from 9.38% to 0.62% whilst increasing unnecessary X-rays from 24.15-34.05% (Table 3).

Table 3: Outcomes of clinical guidelines.

	Placement Errors	Unnecessary X-ray
pH ≤5.5 feed; X-ray everyone with pH>5.5	9.38%	24.15%
pH ≤4 feed; X-ray everyone with pH>4	0.62%	34.05%
X-ray everyone	0	75%

One criticism of our recommendation of lowering the pH cut-off is that X-ray facilities are not widely available and therefore lowering the pH may lead to feeding delays and potential harm from lack of nutrition.[6] Another criticism surrounds the liability of chest radiographs to be misinterpreted. Reducing the pH cut-off used for tube aspirate pH testing may expose patients to a risk of inadvertent feeding if the consequent increase in radiographs to check tube position is associated with an accompanying increase in X-ray misinterpretation. This is debatable as misinterpretation of radiographs affects a cohort of patients with a tube aspirate pH between 4.0 and 5.5. Using the current guideline with a higher pH cut-off (5.5), all of these patients will be fed through the tube regardless of the actual tube site. Given a constant rate of tube misplacement, it is not possible to increase the number of inadvertent feeding errors using a lower pH cut-off, regardless of the risk of X-ray misinterpretation.

In terms of using multiple tests instead of a single test, consider safety needs to rule out lung and oesophagus placements. Magnetic guidance can achieve both ends on its own; the best test to be used with aspirate pH is one that is sensitive to oesophageal misplacement. Auscultation has the potential to halve the chance of oesophagus placement, but the method is subject to interpretation errors and is therefore unreliable.

CONCLUSIONS

The key to maximising the safety of NG tube feeding is to rule out feeding into the lung and to minimise feeding into the oesophagus. A critical step to prevent inadvertent administration of enteral feed into the bronchopulmonary tract is reliable confirmation of tube position prior to commencing feeds. There is also the potential for soft tissue trauma caused during incorrect tube insertion. A recent study reports 35 (18.7%)

incidents of pneumothorax among 187 tube misplacements with an associated increase in mortality.[31] Techniques to improve the accuracy of feeding tube insertion such as electromagnetic guidance may prevent both pulmonary tree injury and the consequences of tube malposition. Considering the strength and reliability of available evidence, this research demonstrates the potential of magnetic guidance testing to be the safest option, followed by the pH test with a cut-off of 4.0 or 5.5. A higher cut-off of pH should only be used when the clinicians have an excellent track record and the pH is measured accurately. Overall, the pH test is the safest test when using a cut-off of 4.0.

Footnotes

(*) The conditional probability of a negative finding (e.g. not lung) is the joint probability of the finding and not lung divided by the prior probability of not lung: p(finding|not lung) = (p[finding & stomach]+p[findings & oesophagus]+p[findings & small bowel])/(p[stomach]+p[oesophagus]+p[small bowel]), where p(finding & tube site) = p(finding|tube site)*p(tube site).

(**) The pH findings were defined differently in the BN than in Tables 1 and 2. The BN software (Netica) rendered it impossible to present pH values in terms of cut-offs, e.g. lower or higher than 5.5. We therefore expressed the pH as discrete categories, i.e. ≤4, between 4 and 5, between 5 and 5.5, between 5.5 and 6, and ≥6. In Tables 1 and 2 the probabilities were binary based on the pH cut-off which is how the test is used in reality. These two methods of expression were consistent. p(pH≤cut-off) is the sum of the discrete probabilities accumulated until that cut-off and the p(pH>cut-off) = 1-p(pH≤cut-off).

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DIAGNOSTIC METHODS IN EOSINOPHILIC OESOPHAGITIS: FROM ENDOSCOPY TO THE FUTURE

***Joaquín Rodríguez-Sánchez, Bartolomé López Viedma**

Endoscopy Unit, Department of Gastroenterology, Hospital General Universitario de Ciudad Real, Ciudad Real, Spain
**Correspondence to joakinrodriguez@gmail.com*

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ABSTRACT

Eosinophilic oesophagitis (EoE) is an increasingly prevalent disease in clinical practice. Nowadays it is the most frequent cause of dysphagia in young patients and the second leading cause of chronic oesophagitis. The gold standard technique for diagnosis and monitoring the disease is oesophagoscopy with biopsies, which is not without complications. Due to the lack of consensus on the monitoring of the disease, and the rise of dietary therapies, there has been a significant increase in the number of endoscopies per patient (up to ten). At the present time, non-invasive methods are being developed that make the management of these patients a less invasive and more sustainable strategy.

Keywords: Eosinophilic oesophagitis, endoscopy, eosinophil, activity index, chromoendoscopy, non-invasive diagnostic method.

INTRODUCTION

Eosinophilic oesophagitis (EoE) is defined as an emerging antigen-mediated immune disorder, characterised by symptoms of oesophageal dysfunction and eosinophilic inflammatory infiltrates in the oesophageal wall, despite treatment with high doses of proton pump inhibitors.[1,2] It is the most frequent cause of dysphagia in the population under 50 years old, and the second leading cause of chronic oesophagitis.[3] The estimated prevalence in occidental population is >50 cases per 100,000 inhabitants, and the peak prevalence in men aged between 35-40 years is estimated as >114 cases per 100,000 persons.[4] The physiopathology of this disease resides in a retarded allergic reaction mediated by T helper Type 2 lymphocytes[5] against alimentary antigens, especially to milk and cereals.[6,7] Most patients, especially in adult ages, experience intermittent and progressive dysphagia to solid foods, frequently accompanied by episodes of food impaction, which requires endoscopic desimpaction.[8] It is a disease with a strong genetic basis. It shows overexpression of genes such as *TSLP* gene, encoding the synthesis of thymic stromal lymphopoietin,[9] or *CAPN14* gene, encoding calpain-14 in response to elevated levels of interleukin 13.[10] This entails a high risk of the disease in first-degree relatives of patients with this disease, compared to the general population.

To date, the only accepted method for the diagnosis and follow-up of EoE is endoscopy with oesophageal biopsy (undertaken in at least five samples).[1,2] Although it is not pathognomonic, the presence of pseudo rings, longitudinal lines, or white exudates suggest the diagnosis of EoE.[2] During recent years, there has been a significant delay in the diagnosis of this disease (which is estimated in a media of 4 years), mainly due to the lack of consensus guides for its management and the great interobserver variability for the description of the endoscopic signs.[11,12] This fact contributes to the development of stenosis and therefore to the worsening of the clinical situation of patients.[13] With the objective of solving this deficiency in the diagnosis, a classification that homogenises the endoscopic diagnosis (Endoscopic Reference Score [EREFS] system)[14] has been proposed. Nevertheless, this system has not been evaluated in other centres.

The lack of consensus on the follow-up of this disease makes the patients subject to numerous endoscopic procedures, and more so if they are following dietary therapies, with food reintroduction protocols that require at least ten endoscopies per patient.[6] In young patients the situation is worsened due to the fact that they have to be anesthetised for the procedure, with innate risks for the patient, and its associated economic cost.[15] It is known that oesophageal endoscopy is not without complications, and even more so in this disease, which is associated with an increase in the number of mucosal tearing and perforations.[6,17] This is why there is an urge for the development of diagnostic tools that allow for the non-invasive management of these patients.

This review focuses on the diagnostic methods of EoE and aims to give both a critical overview of the currently available diagnostic strategies, as well as an update on developing techniques for the near future. With this goal, source studies and review articles were identified by systematically searching in three major bibliographic databases (PUBMED, EMBASE, and Scopus) for the period up to July 2014.

ENDOSCOPIC METHODS

White Light Endoscopy

A great variability has been seen in retrospective series describing the endoscopic signs for EoE, a fact that conditions a limited sensibility for its diagnosis.[18] Nevertheless, on prospective series, the presence of endoscopic signs has been demonstrated in 93% of patients with EoE.[19] Therefore, this increment on the detection of endoscopic manifestations, seen on prospective series in regard to the retrospective series, manifests the importance of a careful and protocolled inspection of the oesophagus, as well as the need of a systematic description of the findings. This last point is closely linked to the experience of the endoscopist making the diagnosis of EoE, meaning that inexperienced endoscopists find approximately 55% of the pathologic signs and experienced endoscopists find approximately 78.4%.[12] This interesting fact is mainly due to the variability found in their description. Regarding this, a fair-to-good interobserver agreement was found in the description of the oesophageal lines (k=0, 48) and pseudo rings (k=0, 56), but a lack of agreement was found on the exudates (k=0, 29) and endoscopic signs (k=0, 34).[11]

With the objective of unifying the endoscopic description of EoE, a new system has been proposed. The EREFS created a protocol for the description of the inflammatory signs (furrows, oedema, exudates) and the remodelling (stenosis and rings), punctuating them according to the severity of the manifestations.[14,20] Nevertheless, the correlation of these findings with histopathology has not been widely studied. In this regard, there is an ongoing collaborative study being carried out in Spain (The Spanish Study of Endoscopy and Eosinophils Correlation Assessment),[21] which is trying to correlate the endoscopic findings (according to the EREFS) with the inflammatory activity of the disease. Preliminary results from this study demonstrate a correlation between the inflammatory activity of EoE and the presence of inflammatory signs (furrows and exudates). However, oedema is present in spite of disease remission, a fact that suggests that this sign is indicative of remodelling more than an inflammatory sign in EoE.

Biopsy Samples

The inflammatory infiltrate present in EoE follows a patchy pattern along the squamous epithelium of the oesophagus.[22] This is of particular relevance when analysing the diagnostic rentability of the biopsy, as the size of the sample is only 0.002% of the oesophageal mucosa.[23] In this regard, it has been shown that when using a cutting point of ≥15 eosinophils/high power field (hpf), the increase in sensibility for the diagnosis of EoE is correlated with the number of biopsies obtained (sensibility of 73% for one biopsy, and of 100% for six biopsies).[24] Therefore, a greater number of biopsies means increased diagnostic yield. In fact, nowadays, the number of biopsies recommended by experts is eight (four for the proximal third and four from the distal third).[22,23] Moreover, biopsy sampling has been shown to be useful to indirectly evaluate the signs of remodelling of the oesophageal wall by detecting the loss of elasticity during the biopsy, known as the 'tug sign'.[25] On the other hand, it is interesting to know that ≥15 eosinophils/hpf is not an uncommon finding in patients with gastroesophageal reflux disease (GERD). Also, in biopsy samples, we can find some histologic signs that suggest the diagnosis of EoE (degranulated eosinophils, diffuse intraepithelial distribution of eosinophils, and eosinophilic microabscesses; Table 1).[26]

Table 1: Histologic signs of eosinophilic oesophagitis (EOE) and gastroesophageal reflux disease (GERD).

Histological sign	EoE	GERD
Degranulated eosinophils	Prominent	Rare
Eosinophilic microabscesses	Frequent	Uncommon
Diffuse intraepithelial distribution of eosinophils	Prominent	Rare (usually limited to the lower half)
Basal cell hyperplasia	Prominent (usually >50% of epithelial thickness)	Mild (usually <25% of epithelial thickness)
Keratinocyte vacuolation	Possible	Possible
Dilated intracellular spaces	Possible	Possible
Lamina propria fibrosis	Frequent	Rare
Lamina propria papillae	May reach upper one-third of the squamous epithelium	May reach upper one-third of the squamous epithelium

Modified by Ali et al.[26]

Chromoendoscopy

Due to the lack of agreement in the anatomic description of white light, the development of chromoendoscopic techniques seems obvious. Nevertheless, this idea has not been sufficiently evaluated, with only one study demonstrating how the application of indigo-carmine on the oesophageal surface with a catheter spray improves the visualisation of the typical endoscopic signs of this disease.[27] Directly opposing what happens in other, similar pathologies, are the optimal visualisation of the mucosa pattern, which are key for the diagnosis. Virtual chromoendoscopy with narrow band imaging (NBI) (Olympus®) without magnification has not been able to improve the diagnostic yield of white light endoscopy.[11] Although, it has recently been published that NBI with magnification can be useful in EoE,[28] being able to differentiate between three specific signs that are not detected with GERD is important: beige discolouration of mucosa, increased and congested intrapapillary capillary loops, and invisibility of submucosal vessels.[29] Other methods of virtual chromoendoscopy, lsuh as Fujinon intelligent colour enhancement (Fujinon®) and I-scan (Pentax®), have not been used for this pathology; I-Scan is currently under evaluation by our group.

Endoscopic Ultrasound (EUS)

The role of endoscopy for the management of EoE has barely been evaluated, and this is one of the reasons why it is not recommended as a first-line tool for the diagnosis and management of EoE[30] by the clinical guidelines of the American College of Gastroenterology. Nevertheless, it is known that tissue changes, such as epithelial hyperplasia, subepithelial fibrosis, and smooth muscle hypertrophy[31] that occur in EoE as a consequence of chronic eosinophilic eosinophilia, can be evaluated by EUS. High-resolution EUS (HR-EUS) has demonstrated its efficacy in the evaluation of the different layers of the oesophageal wall.[32] It has also been possible to verify by HR-EUS that the total wall thickness in patients with EoE is greater than in a control group (2.8 mm versus 2.1 mm; p=0.004), mainly because of a greater mucosal and submucosal layer, given that the circular muscle remains with a similar thickness between groups.[33]

This thickening of the wall has been confirmed in posterior series of patients,[34,35] even though this was without any statistically significant differences due to the small size of the cohort. Therefore, and given that it has recently been manifested that the response to treatment implies an improvement on subepithelial fibrosis,[36] EUS could allow us to objectively evaluate such correlation in isolated cases following an 8-week course of fluticasone (Flonase®),[28] although it would remain to quantify such correlation to evaluate response.

EUS does not only evaluate morphological changes of the oesophageal wall, it also evaluates functional alterations that come as a consequence of fibrotic remodelling phenomena. Using high

frequency probes, it has been found that there are significant functional changes on the longitudinal fibres of the oesophageal muscles, with a marked decrease on the amplitude and duration of their contractions in patients with EoE - another reason why EUS could also play a role in monitoring the functional response to different therapeutic strategies.[37] Anecdotally, EUS fine needle aspiration (EUS-FNA) has also allowed the description of histological findings associated with EoE, such as the existence of subcarinal lymphadenopathies as a consequence of the eosinophilic infiltration[38] or the existence of atypical cells without eosinophils in the oesophageal wall.[39]

Novel Oesophageal Imaging Methods

Confocal laser endomicroscopy is a novel technology capable of obtaining microscopic images of the gastrointestinal tract *in vivo* with the help of intravenous or topical fluorescein.[40] This is an attractive approach to EoE as it spares the patient from biopsies, meaning that it is a less invasive diagnostic technique. It has also demonstrated utility in the detection of adenocarcinoma over Barrett's oesophagus (BO),[41] and it has successfully been tested in the description of a case of EoE.[42]

A modality of reflectance confocal microscopy, denominated spectrally encoded confocal microscopy (SECM), is capable of obtaining images in a more agile way, and without the administration of contrast.[43] It has been able to demonstrate, by the visualisation of biopsies of patients with EoE, a very good correlation with the results obtained by conventional histology ($r=0.76$; $p<0.0001$) with a sensitivity and specificity of 100% for its diagnosis, taking as a reference ≥15 eosinophils/hpf.[44] Applying this technology to the clinical practice, a confocal microscopy capsule has been designed, in a size that makes it easy to swallow (7x33 mm). This device is capable of visualising, *in vivo*, the oesophageal epithelium of a swine.[45] Therefore, taking into account the good correlation between SECM and conventional histology, the development of this device seems an attractive tool as a non-invasive method to monitor EoE.

Multi-photon microscopy (MPM) is an imaging system capable of capturing fluorescence from tissues, and it has been used in vivo to visualise squamous epithelium in animals.[46] Taking advantage of the auto-fluorescence capacity of the eosinophil granule proteins,[47] it has successfully been tested for the detection of eosinophils in the biopsies of patients with EoE.[48] It has to be noted that the applicability of this technique in the follow-up of EoE is subject to the development of probes of MPM, that can be used in the clinical practice.

Optical coherence tomography (OCT) is one of the promising non-invasive *in vivo* optical imaging modalities capable of providing three-dimensional micro-structural information in real-time with micron-scale resolutions and 1-2 mm penetration depth in biological tissues,[49] which has demonstrated its capacity in the histological study of gastrointestinal tract mucosa of mice.[50] Recently, OCT has been evaluated on a murine model of EoE, detecting a thickening of the epithelium when compared with white-mice.[51]

NON-ENDOSCOPIC METHODS

Biochemical Markers

With the purpose of finding serological markers of this disease, total immunoglobulin E levels have been studied, with uneven results. That is, elevated levels on a varied percentage of cases.[52] This may be due the existence of atopic comorbidities in this particular type of patient, which does not behave as a marker of active disease.[53] Eosinophil-derived proteins, such as the eosinophil-derived neurotoxin and the major basic protein, have demonstrated their utility as markers of disease of tissue activity.[54,55] Nevertheless, the cationic protein of the eosinophil does not seem useful as a marker of EoE activity.[53,56] On the other hand, the eosinophil count in serum could behave as a marker of activity of the disease, but care should be taken during pollination seasons when interpreting results, given that this can influence results in patients sensitised to respiratory allergens.[53]

Radiology and Nuclear Medicine

It has been known for years that EoE shows alterations in the barium oesophagogram,[57] but its use is not recommended as a diagnostic tool by the consensus guidelines[2] as 50% of the cases can be normal.[58] Nevertheless, the use of a non-invasive tool for follow-up has been proposed. On this matter, a study has demonstrated a 50% decrease in the calibre of the oesophageal light in adults with EoE when compared to healthy controls. In spite of no differences being found on the maximal and minimal diameter of the oesophagus before and after treatment, a significant increase on the calibre was

seen in those patients that showed alterations on the basal epidermolysis bullosa.[59] Eosinophils granule mayor basic proteins have the capacity to join anionic heparin,[60] and its activity can be detected by SPECT imaging (using 99mTc-Heparin). This tool has been used with success to monitor the inflammatory activity of the disease by incubating the biopsies of patients with active and inactive disease after a diet.[61]

Exhaled Nitric Oxide

Fractional exhaled nitric oxide (FeNO) has been evaluated as a tool to monitor response to treatment in asthma both in children and adults, with varied results.[62,63] It has also been tested as an activity marker in EoE, with significant differences in FeNO levels pre and post-treatment (20.3 ppb [16.0-29.0 ppb] versus 17.6 ppb [11.7-27.3 ppb]; p=0.009). Nevertheless, it did not predict response to treatment to corticoids[64] and, therefore, its role as a non-invasive monitoring tool in EoE is still to be demonstrated.

Luminal Fluids and Oesophageal Cytology

The Enterotest (HDC Corporation, Pilpitas, CA, USA), is a minimally-invasive string-based technology composed of a capsule with approximately 90 cm of string, that was originally designed to detect *Helicobacter pylori* and other small intestine pathogens.[65] With this device, an oesophageal string test (OST), that extracts intraluminal oesophageal secretions and determines eosinophil-derived protein biomarkers, has been designed. This tool has been found to be efficient in the diagnosis of EoE and the monitoring of its activity.[66]

Oesophageal cytology is a method that has been scarcely studied, as it has only been developed for the diagnosis of oesophageal candidiasis. This technique could suppose a less invasive method for the evaluation of this disease as it would not be necessary to take a biopsy sample, and therefore would avoid the possible bias intrinsic in the latter, mainly due to the typical patchy infiltrates that have been previously mentioned. Another advantage of this method is that it provides an immediate diagnosis and an immediate determination of the inflammatory activity, which is particularly useful in patients with dietary therapies found in food reintroduction protocols.

Regarding this last point, our group is currently developing an oesophageal aspirate technique, whose preliminary results show a good cytology/histology correlation to assess the activity of the disease (Rodríguez-Sánchez and García Rojo. Unpublished data). The main inconvenience of this technique is how difficult it is to obtain cytology samples from the oesophagus with endoscopic devices. Therefore, it is interesting to develop devices such as cytosponge, which allows taking a cytology sample from the oesophageal wall after being swallowed like a string-capsule and freed in the stomach. This has proven to be useful in the follow-up of BO[63] and it has been successfully tested in a group of patients with EoE.[67, 68]

CONCLUSIONS

EoE is an emerging clinical entity that forces gastroenterologists to be familiarised with the constant advances in its diagnosis and management in order to correctly approach this pathology that has a high impact on the quality of life of those who suffer it. The current consensus guidelines recommend oesophagoscopy with biopsy (at least five samples) as a technique for the diagnosis and monitoring of the disease. So, the use of dietary therapies carries serial endoscopic explorations that cause high sanitary costs and risks in patients. For the diagnosis of EoE, when the accuracy of endoscopy without biopsies is assessed, we find that the main drawback is the significant interobserver variability when describing endoscopic signs. This fact makes chromoendoscopy unsuitable as a diagnostic method.

EUS could play an important role in evaluating the structural and functional impairment of the oesophagus; however, until today, it is not able to assess the inflammatory activity of the disease. Other less invasive methods, such as OST and oesophageal cytology may be attractive for non-invasive monitoring of EoE. Nevertheless, it should be tested in a larger series of patients and in different centres before adopting them as techniques of choice. Therefore, it is of prime importance to optimise and individualise the diagnostic resources focusing on the search of less invasive techniques with maximal effectiveness in the management and monitoring of the disease.

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UPDATE ON BARRETT'S OESOPHAGUS

Claudia Tarlarini,[1] Enzo Grossi,[2] *Silvana Penco[1]

1. Department of Laboratory Medicine, Medical Genetics, Niguarda Ca' Granda Hospital, Milan, Italy
2. Centro Diagnostico Italiano, Milan, Italy
**Correspondence to silvana.penco@ospedaleniguarda.it*

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ABSTRACT

Barrett's oesophagus (BO) is a precancerous lesion associated with the development of oesophageal adenocarcinoma (OAC). Although different types of metaplasia have been described in BO, only the presence of intestinal metaplasia with goblet cells seems to be indispensable for an accurate diagnosis. Surveillance in BO is still controversial and, to date, the endoscopic screening is recommended only for patients who have at least one risk factor for OAC in addition to chronic gastroesophageal reflux disease (GERD), including being 50 years of age, male gender, Caucasian ethnicity, hiatal hernia, increased body mass index, intra-abdominal distribution of fat, nocturnal reflux symptoms, and tobacco use. Moreover, genetic factors play an important and critical role in the development of BO. In particular, genes related to inflammation, DNA repair, and xenobiotic metabolism have been investigated. To date, relatively little is known about the mechanisms that confer susceptibility to BO carcinogenesis even though several risk factors, genetic and acquired, have been identified. Since BO is a complex disease we support the use of advanced intelligent systems to integrate all the variables involved in this complex pathology and in its progression to cancer. In this review we summarise some of the most interesting controversial topics about the diagnosis, pathogenesis, management, and treatment of BO.

Keywords: Barrett's oesophagus, pathogenesis, management, clinical features.

BARRETT'S OESOPHAGUS (BO) OVERVIEW

BO is defined as a change in the tissue lining the oesophagus. In this condition the normal squamous epithelium (SE) of the oesophagus is replaced with specialised columnar-lined epithelium, a type of tissue that is very similar to the intestinal lining. This process, called metaplasia, usually depends on the gastroesophageal reflux disease (GERD), and it is thought to be an adaptation to chronic acid exposure from reflux since columnar cells are more resistant to acid than squamous cells. After BO identification, patients should undergo a periodic surveillance endoscopy in order to identify early dysplasia: the best histological markers for cancer risk. Different studies have established an association between the presence of BO and the risk of progression to the oesophageal adenocarcinoma (OAC). Indeed, the medical significance of BO is its strong association (about 0.5% per patient-year) with OAC, very often a deadly cancer.[1,2] The prevalence of the disease varies from 0.45-2.2% in patients who undergo upper endoscopy and is >12% when the indication is for reflux symptoms. The prevalence has progressively increased in recent years, mainly in the Western world, where it is actually higher at 5.5%.[3-5] The male/female ratio for BO patients is about 5:1; the difference in distribution of fat among men (more central) and women (more peripheral) may explain the increased risk observed in males.[6]

Symptoms, Diagnosis, and Definition

BO does not have any specific symptoms, but BO patients may have symptoms related to GERD. Currently, diagnosis is made by an upper oesophagogastroduodenoscopy (OGD) and biopsy. The OGD allows detection of the metaplastic columnar epithelium that is characterised by a

particular salmon-pink colour and a coarse texture in the distal oesophagus extending up from the gastroesophageal junction (GEJ), compared with the pale, glossy features of the normal tissue of an oesophagus (Figure 1).[7] Endoscopy detects most, but not all, cases of BO because of the individual variations in the anatomy of the oesophagus and the differences in the squamocolumnar junction location in patients with BO. During the OGD, a biopsy is performed; guideline recommendations provide four quadrant biopsies every 2 cm for nondysplastic BO, as well as four quadrant biopsies every 1 cm for dysplastic BO.[8] However, this protocol investigated only a small portion of metaplastic epithelium (5%) and skipped areas with ambiguous and unapparent BO.[9]

The histological spectrum of BO includes one or a combination of three types of columnar epithelium: gastric fundic-type, junctional-type, and specialised intestinal metaplasia (SIM).[10] SIM means intestinal metaplasia with goblet cells, this is the oesophageal epithelial type usually associated with OAC, and has been considered the precondition for BO diagnosis in past years.[8] In the USA, the presence of intestinal goblet cells is widely accepted as a BO diagnostic criterion, even if this definition could recently include the presence of columnar-lined oesophagus without goblet cells. Once the diagnosis is confirmed, it is the difficult task of the pathologist to distinguish whether or not dysplasia is present and even the different grade of dysplasia.[11] The American Gastroenterological Association[8] has defined BO as: "The condition in which any extent of metaplastic columnar epithelium that predisposes to cancer development replaces the stratified SE that normally lines the distal oesophagus."[12]

Screening Strategies

Screening modalities to detect epithelial changes could be divided into endoscopic and non-endoscopic. Specifically, BO can be diagnosed by endoscopic biopsy, endoscopic white-light visual inspection, or high-definition endoscopy (chromoendoscopy) - a newer endoscope with trimodal imaging capacity. However, white-light endoscopy, as well as chromoendoscopy, is expensive and unsuitable for a population-based screening. Therefore, transnasal endoscopy is a cheaper alternative strategy that is well tolerated and specific in BO detection.[9] Recently, new molecular imaging technologies have been developed. Sturm et al.[13] have produced a peptide that binds specifically to BO presenting with high-grade dysplasia (HGD) and BO associated OAC. This peptide proved to be quite safe and useful for addressing both tissue biopsies and the early detection of BO.[13] New advances have been studied in order to detect precancerous lesions, reducing invasive diagnostic examinations such as targeted imaging with novel fluorescent dye, next generation molecular imaging with proteomics, and novel biomarkers.[14-16]

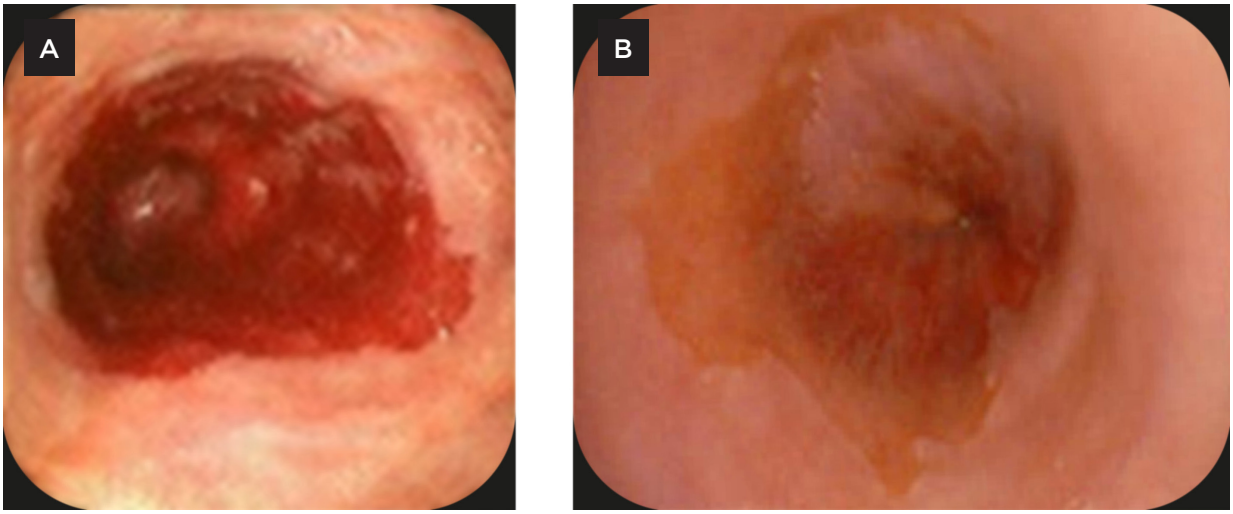

Figure 1: Endoscopic images of Barrett's oesophagus.
A) Great evidence of salmon-pink colour in metaplastic columnar epithelium; B) slight difference of staining between squamous and columnar epithelium.

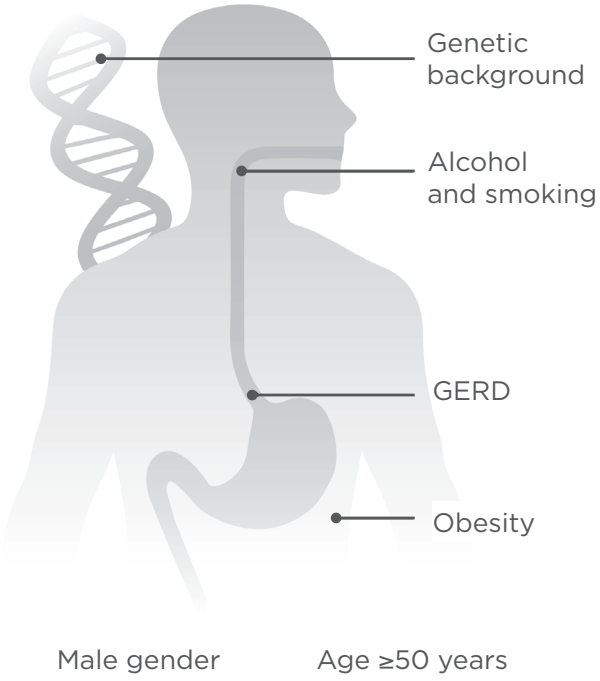

Figure 2: Some of the major risk factors for Barrett's oesophagus.
GERD: gastroesophageal reflux disease.

Among non-endoscopic strategies, we focus on a capsule sponge device (Cytosponge) that has been recently approved by the Medical Health Regulatory Agency in the UK;[17] it consists of a polyurethane sponge, contained within a gelatin capsule, which is attached to a string. To clearly distinguish Barrett's cells from normal cell population, the device is coupled with trefoil factor 3, an immunohistochemical diagnostic biomarker of BO.[17,18] Kadri et al.[19] demonstrated that the Cytosponge test is simple, safe, and well tolerated by patients; the sensitivity and specificity for BO segments of 1 cm or longer are 73.3% and 93.8%, respectively.[19]

Risk Factors

According to the latest guidelines the endoscopic screening for BO may be appropriate only for patients who have at least one risk factor for OAC, in addition to chronic GERD, including being 50 years old, male gender, Caucasian ethnicity, hiatal hernia, increased body mass index (BMI), intra-abdominal distribution of fat, nocturnal reflux symptoms, and tobacco use (Figure 2).[8,12,20,21]

GERD

GERD is the most important risk factor for BO, 5-10% of these subjects develop BO.[22] GERD is a chronic form of gastroesophageal reflux, characterised by regurgitation of stomach contents back into the oesophagus. Acid reflux can cause heartburn, a burning sensation in the midchest, behind the breastbone, or in the upper part of the abdomen, and damage the cells in the oesophagus, causing difficulty swallowing (though this is rare). The features of GERD are different according to short-segment BO (SSBO <3 cm) or long-segment BO (LSBO >3 cm). Approximately 50% of patients with SSBO do not show any GERD symptoms[5] or have symptoms for only a short duration. Conversely, patients with GERD in LSBO tend to have a longer duration of reflux symptoms; in addition 40% of OAC patients have no history of GERD.[23]

Obesity

A strong positive association between BMI and the risk of OAC has been reported;[24] a stronger association of OAC with central abdominal obesity than BMI alone, and a strong association between central obesity and BO has been reported too.[25,26] Central obesity may predispose to GERD by increasing intra-abdominal pressure, and obesity may alter circulating levels of pro-proliferative factors so as to promote oesophageal carcinogenesis.[27] Inflammatory cytokines attract infiltrating immune cells,

which will produce other cytokines, inducing chronic inflammation systematically.[28]

Alcohol and smoking

Different studies on smoking and BO/OAC have shown contradictory results: a greater number of smokers were identified in BO patients compared to the population-based controls; in addition, a dose-response effect linked to cigarette consumption was present.[29] Conversely, Smith et al.[30] found that smoking was associated with an increased risk of BO and BO with dysplasia, but no dose-response effect was found. Other small studies found no clear association.[31] BO studies have generally reported null findings for alcohol consumption; however, results among studies reporting beverage-specific effects have been conflicting. While some have reported an inverse association with wine consumption, others have found lower risk associated with beer, and some evidence for higher risk associated with liquor.[32] These contrasting findings may be due to measurement error; one study captured lifetime alcohol exposure, whilst others used recent alcohol exposure which may be affected by disease status in case–control studies. In one study only wine seemed to be protective[33,34] and perhaps constituents of wine may prevent metaplastic progression to cancer.[35]

Human papillomavirus (HPV)

HPV has been previously investigated in aetiology and progression of BO and OAC with either negative data or positive results of doubtful clinical/aetiological significance.[36,37] Recently, a discovery of a strong association of transcriptionally active high-risk HPV with Barrett's dysplastic tissue has been demonstrated; in addition, viral cancer protein activity was detected more frequently with disease progression. The results strongly indicate that HPV is a common denominator in a significant proportion of pre-malignant oesophageal tissue (Barrett's dysplasia [BD]) and oesophageal cancer.[38]

Genetic risk factors

Several genetic studies have been performed to identify different genomic regions or candidate genes associated with BO.[39-42] Genes related to inflammation, DNA repair, and xenobiotic metabolism have been associated with risk of BO.[43] In 2012, the first genome-wide association (GWA) study on BO was performed in the UK, comprising 1,852 cases and 5,172 controls in the discovery stage and 5,986 cases and 12,825 controls in the replication stage. This study identified two single nucleotide polymorphisms (SNPs) associated with BO: on chromosome 6p21 (rs9257809), within the major histocompatibility complex locus, and on chromosome 16q24 (rs9936833), a locus near the *FOXF1* gene that is involved in oesophageal development and structure.[44] In 2013, another group carried out, for the first time, a GWA of OAC together with the precancerous lesion BO: three new associated loci have been identified. The first, on chromosome 19p13 (rs10419226), is associated with oncogenic activity. The second, in *BARX1* gene, on chromosome 9q22 (rs11789015), encodes a homeobox transcription factor involved in oesophageal differentiation. Finally, the third, in *FOXP1* gene, on chromosome 3p14 (rs2687201), regulates the oesophageal development. The authors conclude that much of the genetic basis for OAC lies in the development of BO, rather than in its progression from a precancerous lesion to cancer.[45] Very recently, Ren and colleagues[46] identified three SNPs and one haplotype in the *CDK1* gene, as well as two SNPs in the *CDK2* gene associated with BO.

Protection Factors and Prevention

Helicobacter pylori

H. pylori infection as well as a 'healthy' diet may decrease the risk of developing BO.[47] Likely *H. pylori* infection decreases gastric acid secretion and thus prevents the development of GERD.[48] While the bacteria damages the stomach and the tissue in the duodenum, some researchers believe the bacteria can actually make the stomach contents less damaging to the oesophagus when GERD is present.

Chemoprevention

Two of the most important strategies to reduce the risk of conversion from BO to OAC are the acid suppression and the modulation of the proinflammatory mechanisms. A wide meta-analysis of 1,813 patients with OAC revealed a greater protective effect of aspirin compared with nonsteroidal anti-inflammatory drugs.[49] Furthermore, a protective role in progression to cancer has also been suggested for statins, and a synergistic role of statins and aspirin in reducing the incidence of OAC in patients with BO has been hypothesised.[50] The AspECT trial,[51] which will be completed in 2019, has recruited 2,500

patients to undergo treatment with aspirin and esomeprazole, a proton pump inhibitor (PPI). Up to now, the treatment appears to be well tolerated and without many side-effects.[51]

Endoscopic surveillance

Dysplasia remains the only validated marker for identifying BO patients at risk, and forms the basis of OAC surveillance. Gaddam et al.[52] recruited a large cohort of 1,401 patients with non-dysplastic BO who were followed-up for ~5 years; the risk of cancer decreased over time, with every subsequent endoscopy, from 0.32% in patients with only one surveillance to 0.11% for patients who had five endoscopies. The largest BO study in the world, the BOSS study,[53] is randomising 3,600 individuals with BO in the UK to evaluate the effectiveness of the surveillance endoscopy; the results are still ongoing.

Artificial Neural Networks and Genetic Predisposition to BO

Relatively little is known about the mechanisms that confer susceptibility to BO carcinogenesis, and the data available are rather controversial due to different methodological issues (e.g. inappropriate control group, lack of population-based DNA collections, small study size, etc.). These findings prompted us to carry out a genetic study.[54] 74 BO patients and 67 controls coming from 6 gastrointestinal (GI) Italian units were evaluated for 6 polymorphisms in 4 genes: *XPC*, *XPD nucleotide excision repair* (*NER*) genes, *XRCC1* (*BER* gene), and *glutathione S-transferase P1*.

Table 1: Some of the genes implicated in the development of Barrett's oesophagus.

Gene Symbol	Gene Name/Description	Expression
ACTA2	Actin, α2, smooth muscle, aorta	+
BMP4	Bone morphogenetic protein 4	+
CDX1	Caudal-type homeobox 1, transcription factor	+
CDX2	Caudal-type homeobox 2, transcription factor	+
COX2	Cyclooxygenase-2, prostaglandin synthesis	+
CCND1	Cyclin D1, cell cycle protein G1-to-S transition	+
COL5A2	Collagen, Type 5, α2, fibrillar collagen molecule	+
EGFR	Epidermal growth factor receptor, transmembrane glycoprotein kinase	+
GATA4	GATA binding protein 4	+
GATA6	GATA binding protein 4	+
HNF1α	Hepatocyte nuclear factor 1 α	+
HNF3 (α,β, γ)	Hepatocyte nuclear factor 3 α, β, γ	+
HNF4α	Hepatocyte nuclear factor 4 α	+
IL-1β	Interleukin 1β, cytokine produced by activated macrophages	+
KLF4	Kruppel-like factor 4, zinc finger-containing transcription factor	+
LGR5	Leucine-rich repeat-containing G protein-coupled receptor 5	+
POSTN	Periostin, osteoblast-specific factor	+
SHH	Sonic hedgehog	+
SOX9	SRY (sex-determining region Y) box 9	+
CDH1	E-cadherin	-
CDKN2A (p16)	Cyclin-dependent kinase inhibitor 2A	-
PAX9	Paried box gene 9	-
SOX2	SRY (sex-determining region Y) box 2	-
TP53	Tumour protein p53	-
TP63	Tumour protein p63, transcription factor	-

Smoking status was analysed together with the genetic data. Since the linear correlation among genetic variants distribution and BO diagnosis was extremely low, with no R-squared values higher than 0.02, we decided to employ for data analysis artificial neural networks, particularly suitable to handle non-linear relations among variables, rather than classical statistical tests. Using artificial neural networks, it was possible to explain two-thirds of the variance related to cases, and control difference through the adaptive selection on nine polymorphisms, with a sensitivity near to 80%.

Molecular Pathogenesis

The metaplastic conversion of SE to specialised columnar epithelium in the distal oesophagus may originate from two different mechanisms.[55] Transdifferentiation seems to be wrong, since new SE can develop after ablation treatment in which the BO epithelium has been completely removed.[56] The best pathogenic hypothesis regarding BO is likely the altered differentiation of stem cells.[57] Different experimental data support four potential origins of these altered metaplastic stem cells: SE, GEJ, the neck, and bone marrow.[58,59] In addition, acid and bile salts, alone or together, might also be involved in the pathogenesis through an increase in reactive oxygen species, causing oxidative stress that results in DNA damage and cell death.[60,61] Chen and colleagues[62] suggest that when gastroesophageal stem cells are stimulated by GERD, the squamous differentiation programme may be inactivated through a loss or downregulation of squamous transcription factors; at the same time the overexpression of the transcription factors related to intestinal development may be activated (Table 1).

Experimental Models

In recent years, different approaches have been used to find a model for BO, but as of yet, no one model offers an ideal system for the study of environmental exposure, genetic risk, and prevention strategies. Cell culture based methods lack the complexity of a multicell system and this aspect can be overcome through the use of organotypic culture that mimics the *in vivo* interplay between the epithelium and underlying stoma. However, animal models provide a better solution to study such a complex disease since they offer the opportunity to evaluate clinical and environmental risk factors in a controlled setting. Furthermore, since several genes and pathways have been implicated in the development of BO, genetic manipulation can also be applied. Mouse, rats, dogs, opossum, guinea pigs, baboons, and pigs have all been used to study BO; however, the lack of spontaneous development of BO in animals presents a strong limitation.[63]

Treatment

The target of treatment is the control of reflux symptoms in order to stop the impairment of the oesophageal lining. This goal could be achieved through a dietary change, removing foods that increase the risk of reflux (e.g. chocolate, coffee and tea, peppermint, orange juice). Alternatively, the use of acid-suppressing medications (PPIs, e.g. omeprazole, lansoprazole, pantoprazole) can be applied. Although the acid suppression is important, the dose to use is still controversial.[8,64] Recently, while continuous PPI therapy may be a symptomatic treatment at best, it could potentially promote dysplastic progression and adenocarcinoma, rather than prevent it.[65] A recent study observed an increased risk for developing HGD and adenocarcinoma in the oesophagus with long-term PPI usage. Therefore, PPI may not protect against malignant progression in BO patients and in selected high-risk patients, and clinicians may consider adding or replacing long-term medical treatment with other modalities.[66] Anti-reflux surgery (ARS) may be considered for people with GERD symptoms. This therapy seems to promote the resolution of BO metaplasia; a meta-analysis demonstrated that 15.4% of patients who had undergone ARS had a regression of BO, compared with 1.9% of patients who were medication treated.[67] In some papers the ARS is even associated to a lower cancer risk progression.[68,69] Dysplasia is the typical precursor of OAC in BO patients and some studies have demonstrated that surgical or endoscopic removal of the dysplastic tissue can prevent its progression to cancer.[8] In the recent years different endoscopic therapies have been established.

Endoscopic ablative therapies

The procedures most often used are photodynamic therapy (PDT) and radiofrequency ablation (RFA). Complications of PDT technique include stricture formation (nearly 40%)[70] and the risk of buried metaplasia, as a result of incomplete endoscopic ablation procedures that destroy only a superficial layer of Barrett mucosa.[71] RFA uses radiofrequency energy (10 J/s) to inflict a thermal injury which

destroys the mucosa of BO patients. RFA appears as the better treatment in eradicating dysplasia and cancer prevention, with greater simplicity management and fewer serious adverse effects compared with PDT.[7,72] The problems of RFA regarded the recurrence rate of intestinal metaplasia ranging from 0-9%[73,74] to 30%.[75,76] Both PDT and RFA have been proven to be superior to eradicate dysplastic BO compared to routine anti-reflux measures and pharmacological anti-reflux measures in randomised trials. Nevertheless, the relative efficacy and safety of the promising endoscopic ablation treatment modalities remain unclear, since no previous head-to-head comparison of PDT versus RFA exists. In a recent study, the two modalities were compared with regards to complete eradication of BO and BD, adverse events, and costs. Both resulted in successfully eradicating dysplasia in BO. However, the overall success rate of RFA was higher than PDT, and RFA was very well tolerated without any major complications and fewer side-effects.[77,78]

Endoscopic mucosal resection (EMR)

EMR is increasingly being utilised as an alternative to surgery in the management of high-grade intraepithelial neoplasia, intramucosal cancer of the GI tract, dysplasia, and some small, very early-stage cancers of the oesophagus. It is less invasive than surgery and, unlike ablative therapies, it provides tissue for histological assessment. EMR is a technique where a piece of the inner lining of the oesophagus is removed with instruments passed down the endoscope. The most common side-effect of EMR is bleeding in the oesophagus, which is usually not serious. Less common, but more serious, side-effects can include oesophageal strictures (areas of narrowing) that might need to be treated with dilation, and puncture (perforation) of the oesophagus wall.[79-81] Both ablative and mucosal resection are often combined in order to reach a better outcome.

Oesophagectomy

This procedure is associated with high morbidity and mortality and causes detrimental effects on the quality of life. Thus, it should be reserved only for patients in which ablation or resection eradication is not complete or durable, and only when endoscopic screening or surveillance revealed HGD. The risk of progression to cancer in BO patients with HGD is considered high enough to determine an intervention through endoscopic eradication therapy. This method includes the use of one or any combination of endoscopic strategies to remove all of the Barrett metaplasia - dysplastic or not.[8,12] Conversely, the low-grade dysplasia (LGD) data of management are contradictory. One study on 147 patients revealed a risk of neoplastic progression of 85%, whereas another one carried out on 210 patients, described a rate of progression to HGD or cancer of only 1.83% per year.[82,83] After this controversial evidence, the guidelines suggested either a more intensive programme of endoscopic surveillance or endoscopic ablation. In addition the diagnosis of LGD should be confirmed by at least two expert GI pathologists.[8,12] Despite the wide variability for cancer risk in the LGD patients, novel specific biomarkers (e.g. abnormal presence of p53 or a number of dysplastic glands) are able to recognise the patients at risk.[84]

CONCLUSIONS

Even though several efforts have been applied to shed light on this disease, we still lack the opportunity to precisely identify those factors allowing early detection of those patients who will develop cancer. In our experience, on a small number of tested subjects and variables, we successfully applied a different method to build up a model that is able to discriminate amongst cases and controls with 80% accuracy. This finding highlights the importance of new methodological and statistical approaches in handling the complexity inherent to chronic degenerative diseases, such as BO.

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THE MANAGEMENT OF ACUTE UPPER GASTROINTESTINAL BLEEDING: A COMPARISON OF CURRENT CLINICAL GUIDELINES AND BEST PRACTICE

Alison A. Taylor, Oliver C. Redfern, *Marinos Pericleous

Department of Gastroenterology, East Surrey Hospital, Surrey, UK
**Correspondence to pericleousmarinos@gmail.com*

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ABSTRACT

Acute upper gastrointestinal bleeding (AUGIB) is the most common GI emergency, responsible for up to 70,000 hospital admissions in the UK and around 4,000 deaths. The latest UK national audit highlighted inconsistencies in both the management and service provision. Several national and international professional bodies have produced evidence-based recommendations on the management of AUGIB. We carried out a review of the guidance documentation published by four expert bodies including the National Institute of Clinical Excellence, the Scottish Intercollegiate Guidelines Network, the American College of Gastroenterology, and those published in the Annals of Internal Medicine. Consensus is still yet to be reached for initiating blood products in the emergency situation, with some evidence suggesting that liberal transfusion could exacerbate bleeding severity, although there is a lack of large randomised trials. It is widely agreed that prompt endoscopy within 24 hours improves outcomes, but evidence suggests that lowering this threshold confers no additional benefit. Use of proton pump inhibitors both pre and post-endoscopy for non-variceal bleeds is also advocated by professional bodies, with substantial evidence that it reduces the risk of re-bleeding. For patients with suspected oesophageal or gastric variceal bleeding, prophylactic antibiotics and vasopressin analogues are recommended, although guidelines vary on specific regimens. Recent UK and international guidelines provide a useful framework to guide management of patients who present to the emergency department with suspected AUGIB; however, their advice varies in some key areas due to a lack of large randomised trials as supporting evidence.

Keywords: Upper gastrointestinal bleeding, transfusion, endoscopy, proton pump inhibitors, non-variceal bleeding, variceal bleeding, antibiotics, vasopressin.

INTRODUCTION

Acute upper gastrointestinal bleeding (AUGIB) is the most common acute GI emergency and can potentially lead to serious haemodynamic compromise and mortality.[1] Consequently, several national and international guidelines have been developed to promote safe risk stratification and timely management of patients at the emergency department. Anatomically, AUGIB is defined as a frank blood loss from within the GI tract, originating proximal to the ligament of Treitz, i.e. from the oesophagus to the third part of the duodenum.[2,3] Symptomatically, AUGIB presents as haematemesis in the form of fresh blood or 'coffee-ground' vomitus with/without the presence of melaena.[4] AUGIB can also present as haematochezia and would be indicative of an extremely brisk blood loss.[5] Aetiologically, bleeding from the upper GI tract can be categorised into variceal and non-variceal, with 80-90% being secondary to non-variceal causes.[1] The latter include: peptic ulcer disease (20-50%), gastroduodenal erosions (8-15%), oesophagitis (5-15%), Mallory-Weiss tears (8-15%), and arteriovenous malformations/gastric antral vascular ectasia (5%). Other causes, such as highly vascularised tumours of the upper GI tract, make up the remainder.[3,4,6] Variceal bleeding (VB) originates

from gastric or oesophageal varicosities, most commonly in the context of portal hypertension.

The incidence of AUGIB in the UK is estimated at 84-172 per 100,000 patients, equivalent to 50-70,000 hospital admissions, and 4,000 deaths annually.[7,8] The substantial health-economic burden and the impact of this emergency on health services has been explored extensively in the literature.[9] The latest UK national audit carried out by the National Blood Service and the British Society of Gastroenterology (BSG) highlighted inconsistencies in service provision throughout the UK.[10] The 'Scope for improvement' report was published by the Association of Upper GI Surgeons, the BSG, Royal College of Nursing, Royal College of Physicians, and Royal College of Radiologists, and called for the development of services in order to address the heterogeneous management of patients presenting with AUGIB.[11]

METHODS

We carried out a PubMed search and identified several guidelines addressing the management of AUGIB. We have selected four expert key bodies that published guidance on this emergency and reviewed their recommendations. These include the National Institute of Clinical Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), the American College of Gastroenterology (ACG), and those published in the *Annals of Internal Medicine*. Our aim was not to perform a rigorous systematic review of each recommendation, but to compare and contrast the available guidance. Where appropriate, pivotal studies, and the clinical importance of their findings, were also explored.

INITIAL MANAGEMENT

The management and approach to a patient presenting with an AUGIB should initially focus on resuscitative measures in response to a haemodynamic compromise. The circulation can be supported initially with intravenous (IV) crystalloids or colloids; however, prolonged resuscitation with saline should be avoided in patients with VB as this may encourage third-spacing and accumulation of ascites.[2,12] While transfusion of blood products can be life-saving in severe AUGIB, it remains unclear as to what their role is in lesser bleeds.[2] In 2002 the BSG advised transfusion for active haematemesis or the presence of hypovolaemic shock.[13] An AUGIB death is rarely related to the actual haemorrhage, but secondary to coexisting morbidities such as cardiorespiratory disease.[14]

Haemoglobin thresholds for transfusion in AUGIB remain controversial. More evidence is required as to whether a restrictive or liberal transfusion regimen confers the best prognosis.[15,16] A 2010 Cochrane review of three randomised controlled trials (RCTs) concluded that liberal transfusions conferred no benefit to survival and, in fact, there was a trend towards increased risk of re-bleeding and mortality, although this trend was not statistically significant.[17] However, a more recent meta-analysis by Wang et al.[18] analysed the data from four RCTs of restrictive versus liberal transfusion strategies in AUGIB and concluded that restrictive transfusion strategies should be employed.[18] Transfusion of red blood cells in AUGIB is common practice, but it is only the current guidelines on the management of AUGIB from the ACG and *Annals of Internal Medicine* that actually provide haemoglobin cut-offs for the initiation of transfusions. The threshold recommended in non-variceal bleeding (NVB) is a haemoglobin level of <7 g/dL, and for VB <8 g/dL.[12,19,20] The 2012 non-variceal guidelines from the ACG also advise that a higher haemoglobin level may be targeted in patients with significant comorbidities such as coronary artery disease; however, the exact value is debatable and should be tailored to each individual.[12,19,20] Table 1 summarises the current recommendations for the initial management of patients presenting with AUGIB.

Coagulopathy is an interesting area of AUGIB management as it can also be indicative of comorbidities such as liver disease, but there is very little evidence as to how such patients should be managed.[19,21] The guidelines for variceal bleeds from the ACG advise that transfusion of platelets and fresh frozen plasma (FFP) should be considered for patients with a significant coagulopathy, but again no specific thresholds are given (i.e. for international normalised ratio [INR] or platelet count).[12] In contrast, NICE does provide these parameters, but in a prospective national UK audit[22] (in which a coagulopathy was defined as an INR ≥1.5), there was a heterogeneous use of FFP, despite the finding that coagulopathy was associated with a 15% mortality rate.[7,21,23]

Risk Assessment

The presentation of AUGIB can range widely from minor non life-threatening bleeds to tragic

exsanguinations.[24] Initial risk stratification is vital to determine the timing of key interventions such as endoscopy.[25,26] In AUGIB, two main factors determine hospital admission: the need for haemodynamic support and whether endoscopic techniques are required to achieve haemostasis.[27]

Table 1: A comparison of the initial management, risk assessment, and timing of acute upper gastrointestinal bleeding.[2,7,12,20]

	National Institute of Clinical Excellence (NICE) 2012	Scottish Intercollegiate Guidelines Network (SIGN) 2008	American College of Gastroenterology 2012 (Non-variceal) and 2007 (Variceal)	*Annals of Internal Medicine* – Clinical Guidelines 2010 (Non-variceal)
Blood transfusion	Transfusion is recommended. No specific cut-offs.	Blood transfusion should be considered after a loss of 30% of the circulating volume.	Non-variceal: Transfuse to target haemoglobin levels of ≥7 g/dL with higher targets in severe blood loss or co-morbidities. Variceal: Transfuse to maintain haemoglobin of 8 g/dL.	Transfuse when haemoglobin levels ≤7 d/dL.
Correction of coagulopathy	FFP can be used in patients with either a fibrinogen level <1 g/L or a PT (INR)/APTT >1.5-times normal. PT complex concentrate can be given in those patients on warfarin and who are actively bleeding.	Not addressed.	Non-variceal: Not addressed. Variceal: Not addressed.	Correction of coagulopathy for patients on anticoagulants.
Transfusion of platelets	Transfuse when actively bleeding and a platelet count of <50.	Not addressed.	Non-variceal: Not addressed. Variceal: Not addressed.	Not addressed.
Risk scoring tools	Blatchford score initially, then complete Rockall score post endoscopy. Consider discharge if Blatchford is 0.	Use abbreviated and full Rockall score. Consider discharge if score is 0. Endoscopy if score is >0. Consider early discharge for patients with complete Rockall score of <3.	Non-variceal: A Blatchford score of 0 can allow the consideration of early discharge of these individuals without an inpatient endoscopy. Variceal: Risk assessment is not addressed with the use of formal scoring systems.	Both Blatchford and Rockall but there is no definitive statement as to which is recommended.
Timing	Immediate endoscopy unstable patients after resuscitation. Endoscopy within 24 hours for all other patients.	Within 24 hours.	Non-variceal: Within 24 hours. Within 12 hours if signs of shock or other high- risk clinical features. Variceal: Within 12 hours.	Within 24 hours.
Secondary care infrastructure	Not addressed.	Management in a dedicated gastrointestinal bleeding unit.	Not addressed.	Not addressed.

FFP: fresh frozen plasma; PT: prothrombin time; INR: international normalised ratio; APTT: activated partial thromboplastin time.

Several risk classification systems have been developed to guide the timing of intervention and predict clinical outcomes.[26] The Blatchford score includes clinical and serum parameters, which are easily available following initial resuscitation.[24] A prospective study undertaken in four UK hospitals by Stanley et al.[25] showed that this measure can identify individuals presenting with an AUGIB that are suitable for outpatient management.[25] A later study by Pang et al.[27] concluded that a score of 0 can predict low-risk patients with high specificity who can be considered for early discharge.[27] In contrast, the Rockall score combines clinical parameters with endoscopic findings to predict the probability of mortality.[28] It has been subsequently modified to exclude endoscopy results, although it appears to be inferior to the Blatchford score for this purpose.[29] Nevertheless, the full Rockall score has an important role in predicting re-bleeding and mortality and, despite its limitations, remains the most widely used system both in the UK and US.[27,30,31]

Timing of Endoscopy

Evidently, oesophagogastroduodenoscopy (OGD) remains key to the management of AUGIB by providing diagnosis and enabling therapeutic intervention.[27] The severity and the suspected underlying aetiology of the AUGIB influence the urgency for endoscopy.[29,32,33] A 1992 meta-analysis showed that prompt endoscopic therapy reduces the risk of death, re-bleeding, and the need for surgery.[34] However, the urgency of endoscopy has been variably defined in the literature ranging from 2-24 hours after initial presentation.[19] A 1993 audit, led the BSG to recommend that high-risk patients should have endoscopy performed within 24 hours of presentation – a consensus reiterated by all guidelines compared in this review article.[2,7,13,20] NICE further propose that endoscopy should be offered immediately in unstable patients, with the ACG recommending that those patients with features of shock or suspected VB undergo endoscopy within 12 hours.[7,12,20]

A review of RCTs and retrospective studies performed in 2009[35] failed to provide evidence that endoscopy, within a few hours of presentation, impacts mortality or reduces the re-bleeding risk, but advocated endoscopy within 24 hours.[35] Similarly, a recent prospective study of 4,478 patients[22] concluded that endoscopy within 12 hours of presentation did not reduce mortality.[22] In order to meet recommendations, endoscopy units require the infrastructure to provide an emergency service 24 hours per day. A nationwide UK audit carried out in 2007 showed that only 50% of OGDs were being performed within 24 hours, increasing to 55% for high-risk patients.[10] One possible explanation is that only 52% of the participating centres had a formal out-of-hours emergency consultant rota. The audit highlighted the need for dedicated GI bleeding units, consisting of experienced nursing staff and evidence-based protocols. Table 1 summarises the current recommendations regarding risk assessment and the timing of endoscopy.

NVB

Advances in endoscopic and pharmacological therapies in the past few decades have reduced recurrent bleeding, the need for surgery, and mortality from upper GI blood loss.[26]

Proton Pump Inhibitors (PPIs) and Prokinetic Agents

Drugs that modify gastric acid secretion have made a large impact upon the prevention of peptic ulcer disease and outcomes in AUGIB.[21] A 2010 Cochrane review of six RCTs, where an IV PPI was administered on admission, demonstrated that there was a significant reduction in high-risk GI lesions found at endoscopy, signalling a reduced need for therapeutic intervention. There was, however, no significant effect on overall mortality, the need for surgery, or rates of re-bleeding.[36] Both NICE and SIGN do not advocate the use of PPIs prior to endoscopy.[2,7,20]

Administration of prokinetics, prior to endoscopy, is thought to aid visualisation and endoscopic diagnostic yield.[5] Barkun et al.[19] suggested that IV erythromycin or metoclopramide, prior to endoscopy for an AUGIB, decreased the requirement of repeat endoscopy for lesion identification.[19] Nevertheless, the use of these agents has not formed part of standard practice due to the lack of evidence regarding the improvement of clinical outcomes, and it has been agreed that they should be restricted to only those patients with a large volume of blood in the stomach.[5,19,20]

Endoscopic Therapy

The modified Forrest classification is commonly used to categorise the appearances of ulcers found in endoscopy to direct appropriate therapy.[37]

Table 2: Summary of the current recommendations for the management of non-variceal bleeding.[2,7,12,20]

	National Institute of Clinical Excellence (NICE) 2012	Scottish Intercollegiate Guidelines Network (SIGN) 2008	American College of Gastroenterology 2012 (Non-variceal) and 2007 (Variceal)	*Annals of Internal Medicine* – Clinical Guidelines 2010 (Non-variceal)
Pre-endoscopy PPI	Do not give PPI or H2 receptor antagonist.	Do not give PPI.	High-dose IV PPI e.g. 80 mg bolus followed by 8 mg/hr infusion).	PPIs can be used to decrease the need for endoscopic therapy.
Prokinetics	Not addressed.	Not addressed.	Consideration of IV erythromycin infusion prior to endoscopy.	Do not use routinely.
Endoscopic therapy – which lesion?	Not addressed.	Actively bleeding lesions, non-bleeding visible vessels and for those with an adherent clot.	Actively bleeding lesions and non-bleeding visible vessels, adherent clots especially in those patients who may be at greater risk of re-bleeding.	Actively bleeding lesions or visible vessels. Adherent clots at endoscopy can be dislodged with irrigation and then appropriately treated.
Endoscopic therapy – type	Adrenaline monotherapy not recommended. Consider co-therapy with clips, thermal coagulation, fibrin, or thrombin.	Adrenaline monotherapy not recommended. Use co-therapy with adrenaline injection (13 ml of 1:10,000) and clips or thermal coagulation.	Adrenaline monotherapy not recommended. Thermal therapy and sclerosant injection and clips are recommended. For actively bleeding lesions, thermal or adrenaline injection with a second modality would be preferred over clips or sclerosant alone.	Adrenaline monotherapy not recommended. Consider co-therapy with clips, thermal coagulation, or sclerosant injection for high-risk lesions.
Post-endoscopy PPI	Give PPIs in patients with stigmata of recent haemorrhage. PPI type not specified.	High-dose PPIs in major bleeding. Give omeprazole or pantoprazole 80 mg bolus and then 8 mg/hour infusion for 72 hours.	High-dose PPIs when active bleeding, visible vessels, or an adherent clot. Give 80 mg bolus and then 8 mg/hour infusion for 72 hours. PPI type not specified. Other lesions in the Forrest classification can receive once-daily oral PPI.	An IV bolus followed by a continuous PPI. PPI type not specified.
Repeat endoscopy	Consider in patients with high risk of re-bleeding, especially if there is doubt that haemostasis has been achieved. Repeat endoscopy for patients who re-bleed. Consider surgical options for failed haemostasis. Interventional radiology for unstable patients who re-bleed after a 'second look' endoscopy and subsequent therapy.	Endoscopy should be repeated within 24 hours if initial treatment was thought not to be sufficient or if subsequent bleeding would likely result in death.	Not recommended unless there is a re-bleed. Interventional radiology or surgery should be considered for patients who re-bleed after a 'second look' endoscopy and subsequent therapy.	Not recommended unless there is a re-bleed.

PPI: proton pump inhibitor; IV: intravenous.

In this classification, Grade 1 is for active bleeding (1a active spurting, 1b for active oozing), Grade 2 is for those with the stigmata of recent haemorrhage (2a visible vessel, 2b adherent clot, 2c flat pigmented spot), and Grade 3 for lesions without signs of recent haemorrhage.[21,26,38] The size of the ulcer and signs of bleeding have been shown to correlate with the risk of re-bleeding and death.[28] Endoscopic therapy is indicated for Grades 1 and 2a; however, the role in Grade 2b lesions has proved controversial despite the reported 8-36% risk of recurrent haemorrhage.[19,20,38,39] A meta-analysis of five RCTs[40] showed that endoscopic intervention was effective for ulcers with active bleeding or visible vessels, but that the role in those with an adherent clot was uncertain.[40] Conversely, Kahi et al.[39] suggested that endoscopic therapy can prevent re-bleeding in the presence of adherent clots.[39]

A number of modalities for endotherapy can promote haemostasis, including injection, thermocoagulation, and application of mechanical clips.[21,26] The beneficial role of adrenaline injections was demonstrated in the late 1980s with a prospective study[41] which compared injection without other endoscopic therapy, and found that adrenaline significantly improved outcomes.[41] Adrenaline has been popular with clinicians due to its safety profile, ease of use, and cost-effectiveness, but today it is considered inferior to other monotherapies or combination therapies.[39,42-45] A meta-analysis in 2004 of 1,673 patients comparing adrenaline alone with adrenaline and a second endoscopic technique, showed that the additional therapy reduced the re-bleeding rate from 18.4% to 10.6%, and mortality from 5.1% to 2.6%.[42] A more recent Cochrane review further confirmed these findings.[44] A meta-analysis by Yuan et al.[45] suggested that clipping is no more superior to other modalities,[45] and this was also a point made by Laine and McQuaid.[40] This latter study also demonstrated that monotherapy with thermal devices, sclerosants, clips, thrombin, or fibrin glue provides more effective haemostasis than adrenaline alone.

Post-Endoscopy Management in NVB

PPIs

The use of PPIs post endoscopy has been extensively studied, with evidence that a high-dose PPI produces an almost neutral pH within the stomach, favouring haemostasis by enhancing platelet aggregation and clot formation.[1,46] A study comparing high-dose omeprazole (an initial bolus IV injection of 80 mg, followed by an infusion of 8 mg per hour for 72 hours) versus placebo after endotherapy to bleeding peptic ulcers, revealed that PPI substantially reduced the risk of recurrent bleeding.[46] A larger trial using esomeprazole demonstrated a reduction in re-bleeding rates at 72 hours sustained for 30 days.[47] A 2006 Cochrane review of 24 trials also supported the use of PPI therapy after endoscopy. Nevertheless, there remains limited evidence of any reduction in mortality.[48] The standard regimen in the guidelines is the initial bolus of PPI followed by an infusion over 72 hours, and this has been acknowledged in the majority of the non-variceal literature included in this article.

Repeat endoscopy

Despite endotherapy, re-bleeding is common in patients with AUGIB (between 15-20% of patients).[49] Guidelines focus upon whether a repeat endoscopy should be performed prophylactically to ensure that adequate haemostasis has been achieved or whether it should be only utilised following a confirmed re-bleed. Marmo et al.[49] found a significant reduction in re-bleeding compared to a control group who did not undergo repeat endoscopy;[49] however, it should be noted that the trials included in this particular review were published between 1990 and 2000, prior to the routine use of high-dose PPI post procedure, which confers a reduction in re-bleeding in its own right. Nonetheless, a more recent trial[50] comparing re-endoscopy and surgery in re-bleeding found that further endotherapy reduced the need for surgery and was associated with fewer complications.[50] UK guidelines advocate the 'second look' endoscopy in those patients at high risk of a further bleed or if there is potentially inadequate haemostasis at initial endoscopy.[2,7] However, non-variceal guidelines from the US confine its use to those patients who re-present with subsequent haemorrhage.[12,20]

VB

Variceal haemorrhage is due to oesophageal or gastric varices, secondary to portal hypertension conferred by liver cirrhosis. Indeed, oesophageal varices are present in approximately 30-40% of patients with cirrhosis,[51] and bleeding from varices

occurs at an annual rate of 5-15%.[1] Despite the high mortality rate from variceal haemorrhage, there has been a reduction over recent years, most likely precipitated by the use of antibiotic prophylaxis, portal antihypertensives, and effective endoscopic therapy.[51]

Antibiotic Prophylaxis

Bacterial infection is another frequent complication in cirrhotic patients with an AUGIB, present in 25-65% of patients on admission or during their hospital stay,[12,52] and it is believed to promote VB.[53]

Table 3: Summary of the recommendations for the management of variceal haemorrhage.[2,7,12]

	National Institute of Clinical Excellence (NICE) 2012	Scottish Intercollegiate Guidelines Network (SIGN) 2008	American College of Gastroenterology 2012 (Non-variceal) and 2007 (Variceal)	*Annals of Internal Medicine* – Clinical Guidelines 2010 (Non-variceal)
Prophylactic antibiotics	Recommended (No preferred type)	Recommended (No preferred type)	Short-term antibiotic prophylaxis should be given to every patient with cirrhosis. Oral norfloxacin 400 mg BD or IV ciprofloxacin is the recommended regimen. IV ceftriaxone may be used in advanced liver disease or if there are high rates of quinolone resistance.	N/A
Pharmacological therapy	Terlipressin recommended.	Terlipressin recommended.	Pharmacological therapy (somatostatin, terlipressin, octreotide) should be commenced as soon as variceal haemorrhage is suspected and continued for 3-5 days.	N/A
Endoscopic intervention	Band ligation should be used for oesophageal varices. Endoscopic injection of N-butyl-2-cyanoacrylate should be used for gastric varices. TIPS should be considered if variceal bleeding is not controlled by the above measures.	Band ligation should be used for oesophageal varices. Endoscopic injection of N-butyl-2-cyanoacrylate should be used for gastric varices. TIPS should be considered if variceal bleeding is not controlled by the above measures. Balloon tamponade can be considered as a temporary measure if bleeding is failed to be controlled.	Band ligation or sclerotherapy should be used for oesophageal varices. Endoscopic injection of N-butyl-2-cyanoacrylate should be used for gastric varices. TIPS should be considered if variceal bleeding is not controlled by the above measures. Balloon tamponade can be considered as a temporary measure (maximum 24 hours) if bleeding is failed to be controlled.	N/A

IV: intravenous; TIPS: transjugular intrahepatic portosystemic shunt.

Seminal work in 1985 by Rimola et al.[54] first showed that the prophylactic use of non-absorbable, oral antibiotics can significantly reduce the incidence of concomitant infection in cirrhotic patients with AUGIB.[54] A 2002 review concluded that short-term antibiotic use decreased both the rate of infection and mortality – this was evident regardless of the presence of ascites.[55] An updated 2010 Cochrane review further supported the use of antibiotics.[56] Norfloxacin is a poorly absorbed quinolone that was shown to be successful in preventing bacterial infections in cirrhotic patients with GI haemorrhage, and has subsequently been standard for this purpose.[57] However, a study[52] comparing oral norfloxacin with IV ceftriaxone found that the latter was a more effective prophylactic agent in patients with advanced cirrhosis.[52] Regardless of the agent, short-term antibiotic prophylaxis is recommended in the NICE and SIGN guidelines, together with those from the ACG.[2,7,12]

Pharmacological Therapy

Other pharmacological therapies used in VB act to lower the portal pressure and thus reduce the blood flow to the varices. They do not, however, replace the need for endotherapy.[51] Vasopressin is a potent vasoconstrictive agent, but may also affect the blood supply to the myocardium; the high risk for cardiac complications has limited its use in reducing portal pressures. Terlipressin is a synthetic analogue of vasopressin and is less potent. A systematic review of the use of terlipressin in acute variceal haemorrhage found that this particular agent not only controls blood loss, but uniquely reduces mortality.[58] As in-hospital mortality rates from variceal haemorrhage are between 20-50%,[58] it can be seen that terlipressin would appear to be the most appropriate choice as the first-line pharmacological agent. Octreotide (a synthetic analogue of somatostatin) has also been shown to be effective in controlling bleeding, and some authors found that it can be superior to its other vasoactive counterparts in oesophageal bleeding.[59]

A meta-analysis found that the efficacy of endotherapy was significantly improved when used in synergy with vasocontrictors.[60] A later review from D'Amico et al.,[61] comparing sclerotherapy with vasoactive drugs, found no difference in efficacy when looking at the controlling of bleeding, and concluded that they can be safely used as initial therapy prior to endoscopy.[61] The NICE and SIGN guidelines advocate the use of terlipressin in any patient with a suspected variceal bleed, but the guidelines from the ACG specify that either terlipressin, octreotide, or somatostatin should be initiated rapidly in the acute setting.[2,7,12] The differences between the USA and UK in this regard may be due to the differences in drug pricing or licensing between the two countries.[62]

Endoscopic Therapy

Endoscopy remains at the forefront of the current management in VB. The two endoscopic methods available to treat bleeding oesophageal varices are band ligation and sclerotherapy. Endoscopic sclerotherapy has been shown to be a highly effective method of controlling an initial bleed and can halt blood loss in up to 90% of patients.[63] A study of variceal banding versus sclerotherapy reported that banding was superior in terms of the control of bleeding and re-bleeding risk, and also reduced mortality rates.[64] Consequently, band ligation has been recommended universally as the first choice for oesophageal varices in all of the current guidelines, but those from the ACG make the addition that sclerotherapy can be used when banding is not technically feasible.[2,7,12] Gastric varices can be managed by banding, sclerotherapy, or endoscopic injection of the tissue adhesive N-butyl-2-cyanoacrylate. A recent trial comparing banding versus cyanoacrylate injection found that glue injection was more effective at controlling the initial haemorrhage and reducing re-bleeding rates.[65] A similar study showed no difference in terms of the initial haemorrhage control, but found that cyanoacrylate reduced the long-term re-bleeding risk.[66] The endoscopic injection of this adhesive has been adopted as first-line practice on both sides of the Atlantic.[2,7,12]

DISCUSSION

Guideline consensuses for the management of AUGIB still present some uncertainties. With regards to initiating blood products, some evidence suggests that liberal transfusion could exacerbate bleeding severity, although there is a paucity of large RCTs. Conversely, it is clear that prompt endoscopy (within 24 hours) improves outcomes, but evidence suggests that lowering this threshold (e.g. to 12 hours) confers no additional benefit. The use of PPIs, both pre and post endoscopy, for non-variceal bleeds is also advocated by professional bodies, with substantial evidence that it reduces

the risk of re-bleeding. For patients with suspected oesophageal or gastric VB, prophylactic antibiotics and vasopressin analogues are recommended. In summary, recent UK and international guidelines provide a useful framework to guide management of patients who present to the emergency department with suspected AUGIB; however, their advice varies in some key areas due to the lack of large RCTs.

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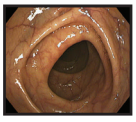

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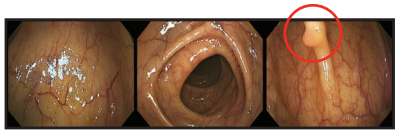

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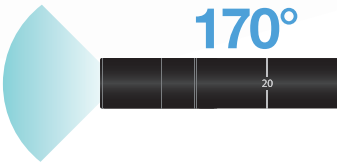

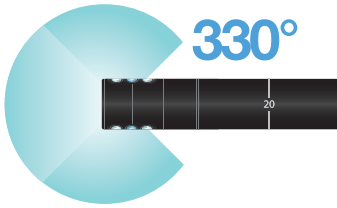

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SMALL INTESTINAL TUMOURS: AN OVERVIEW ON CLASSIFICATION, DIAGNOSIS, AND TREATMENT

Chiara Notaristefano, *Pier Alberto Testoni

Division of Gastroenterology and Gastrointestinal Endoscopy, Vita-Salute San Raffaele University – Scientific Institute San Raffaele, Milan, Italy
**Correspondence to testoni.pieralberto@hsr.it*

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ABSTRACT

The small intestinal neoplasia group includes different types of lesions and are a relatively rare event, accounting for only 3-6% of all gastrointestinal (GI) neoplasms and 1-3% of all GI malignancies. These lesions can be classified as epithelial and mesenchymal, either benign or malignant. Mesenchymal tumours include stromal tumours (GIST) and other neoplasms that might arise from soft tissue throughout the rest of the body (lipomas, leiomyomas and leiomyosarcomas, fibromas, desmoid tumours, and schwannomas). Other lesions occurring in the small bowel are carcinoids, lymphomas, and melanomas. To date, carcinoids and GIST are reported as the most frequent malignant lesions occurring in the small bowel. Factors that predispose to the development of malignant lesions are different, and they may be hereditary (Peutz-Jeghers syndrome, familial adenomatous polyposis, hereditary non-polyposis colorectal cancer, neuroendocrine neoplasia Type 1, von Hippel-Lindau disease, and neurofibromatosis Type 1), acquired (sporadic colorectal cancer and small intestine adenomas, coeliac disease, Crohn's disease), or environmental (diet, tobacco, and obesity). Small bowel tumours present with different and sometimes nonspecific symptoms, and a prompt diagnosis is not always so easily performed. Diagnostic tools, that may be both radiological and endoscopic, possess specificity and sensitivity, as well as different roles depending on the type of lesion. Treatment of these lesions may be different and, in recent years, new therapies have enabled an improvement in life expectancy.

Keywords: Small intestinal neoplasia, hereditary syndromes, adenoma, adenocarcinoma, gastrointestinal stromal tumours, neuroendocrine tumours, melanoma, lymphoma.

INTRODUCTION

The small intestinal neoplasia group includes different types of lesions, either benign or malignant, accounting for only 3-6% of gastrointestinal (GI) neoplasms and 1-3% of all GI malignancies;[1-2] however, the incidence of small bowel primary malignant tumours is currently increasing year by year. Factors that predispose to the development of malignant lesions are different, and they may be hereditary, acquired, or environmental. Hereditary factors include: familial adenomatous polyposis (FAP), Peutz-Jeghers syndrome (PJS), hereditary non-polyposis colorectal cancer (HNPCC), multiple endocrine neoplasia Type 1 (MEN 1), von Hippel-Lindau (VHL) disease, and neurofibromatosis Type 1 (NF1). Acquired conditions associated with an increased risk of small bowel tumours are sporadic colorectal cancer and small intestinal adenomas, coeliac disease, and Crohn's disease. Environmental factors include diet, tobacco, and obesity; greater consumption of red meat, salt-cured and smoked foods, alcohol, and tobacco, and increased body mass index have been hypothesised to be predisposing factors for small intestinal cancer, but studies are still controversial.[3-9]

BENIGN LESIONS

There are different hereditary syndromes related to small bowel lesions:

- FAP: this autosomal dominant condition is caused by the mutation of *APC* gene on chromosome 5. 50% of individuals with FAP present adenomatous polyps of the duodenum, commonly found in the second and third portions. Duodenal adenocarcinoma is the second most common malignancy in FAP or attenuated FAP, with a lifetime risk of approximately 4–12%.

- PJS: is an autosomal dominant condition associated with a mutation of the *STK11* gene. The syndrome is characterised by the presence of small intestinal hamartomatous polyps, melanin spots on lips and buccal mucosa, and increased risk of developing different malignancies (breast, colon, pancreas, stomach, ovarian, lung, testicular, oesophagus). In these patients the cancer lifetime risk is about 13%.[10]

- HNPCC: Lynch syndrome depends on a germline mutation in a class of genes involved in DNA mismatch repair, including *hMSH2*, *hMLH1*, *hMSH6*, and *hPMS2*. Patients have an increased risk of developing different malignancies (colon, endometrium, stomach, ovarian, hepatobiliary tract, urinary tract, pancreas), with an overall cancer lifetime risk of about 1-4%.[11]

- Other familial syndromes are MEN1, VHL disease, and NF1, predisposing to increased risk of carcinoids.[12]

Adenomas

There are different types of adenomas: villous, tubular, and those arising from Brunner's gland. The first one occurs mostly in the duodenum (prevalence 0.4% during oesophagogastroduodenoscopy)[13,14] and has an increased potential for malignant transformation.[15,16] Adenomas arising around the ampulla of Vater represent about 10% of all duodenal adenomas, with a reported autopsy prevalence of 0.04–0.12% and a better prognosis compared with the other malignant ampullary neoplasms involving the pancreaticobiliary ductal system.[17] Ampullomas can be removed by endoscopic resection or surgery, when endoscopic removal is unfeasible (lesions already invasive). Adenomas located distal to the papilla are rare and most of them remain clinically silent until the advanced stages and have been discovered incidentally. Some of them occur in a familial polyposis setting: recent studies have revealed that up to 90% of patients with this hereditary syndrome have polyps in the jejunum and ileum.[18,19] Adenomas may present with anaemia, bleeding, obstruction, or, in case of ampulloma, with obstructive jaundice or pancreatitis.[20,21]

Leiomyomas, Lipomas, and Other

Leiomyomas are mesenchymal tumours arising from smooth muscle layer, usually small (<1 cm), well circumscribed, and submucosal. They are discovered incidentally and consist of bland spindle cells with low or moderate cellularity, mild or no cytological atypia, and rare mitoses.[2] Lipomas usually appear as submucosal, capsulated, yellowish masses protruding into the lumen, often single, and represent about 2.5% of non-malignant tumours of the intestinal tract.[21] Sometimes lesions are ulcerated. Lipomas are generally asymptomatic but melena, bloody stools, abdominal pain, or intestinal obstruction - secondary to intussusception - may occur.[22] Other rare benign lesions are the lymphangioma and haemangioma. Lymphangioma is a rare intra-abdominal tumour, usually identified in childhood; most intra-peritoneal lesions are found in the small bowel mesentery. Haemangiomas are rare lesions that usually present with bleeding.[23]

MALIGNANT LESIONS

The most frequent types of primary small bowel malignancies are adenocarcinoma, stromal tumours, sarcoma, carcinoid tumours, and lymphoma.[24] The incidence of all malignant lesions of small intestine ranges from 0.5-1.5/100,000 in males and 0.2-1.0/100,000 in females.[25] In general, the incidence of small intestine cancer is on the rise but, while in the 1980s the most frequent neoplasms were adenocarcinomas, between 1985 and 2005 the incidence of carcinoid tumours has increased significantly from 27.5-44.3%, while that of adenocarcinomas is slightly decreased from 42.1-32.6%. The proportion of patients with mesenchymal tumours or lymphoma remained almost unchanged. Also, the location of these tumours over these 20 years has changed. In fact, duodenal tumours increased (carcinoid 10.9–22.3%; adenocarcinoma 49.1–58.8%; stromal tumours 10.4–17.2%; lymphoma 10.2–21.7%; $p<0.0001$) with a concomitant decrease in jejunal and ileal malignancies.[26]

Adenocarcinoma

Adenocarcinoma represents about 30-40% of the cancers observed in the small intestine,[27] with the highest incidence in the duodenum, probably

reflecting the higher concentration of bile that increases the risk of adenocarcinoma.[28] The peak of presentation is at 58-70 years and is slightly superior in men than women (58% versus 42%).[24] Risk factors for developing adenocarcinomas are Crohn's disease and, in <10% of cases, inherited syndromes such as HNPCC and FAP.[29-31] The clinical presentation of adenocarcinoma might be non-specific, most frequently: abdominal pain (43%), nausea and vomiting (16%), anaemia (15%), overt GI bleeding (7%), jaundice (6%), and weight loss (3%). In about 10% of cases the neoplasia is asymptomatic.[32]

Neuroendocrine Tumours (NETs)

NETs arise from the cells of the neuroendocrine system[33-35] and produce peptides, neuroamines, and vasoactive substances which lead to many clinical syndromes. 'Carcinoid tumours' originate from enterochromaffin cells of the aerodigestive tract and represent the majority of NETs; they are well differentiated lesions representing about 40% of small intestinal malignancies.[36] Lesions are classified into three groups according to their embryological origin, staining characteristics, and clinical behaviour: foregut (bronchial, gastric, and duodenal), midgut (jejunal, ileal, and caecal), and hindgut (distal colon and rectal) tumours.[36] NETs originate most commonly in the distal ileum, within 60 cm of ileocaecal valve,[37] and about 25% have synchronous lesions.[38] Symptoms are related to the enlarging of the lesion or secretion of vasoactive amines. The most common manifestations are vague abdominal pain (40% of cases)[30] and intermittent bowel obstruction, due to a mechanical obstruction or a desmoplastic reaction by mesenteric lymph-nodes, which, in turn, may lead also to mesenteric ischaemia.[38] Most NETS are indolent but some, even the smaller ones, can metastasise, mainly in the liver, mesentery, and peritoneum, producing the well-known 'carcinoid syndrome', characterised by cutaneous flushing, diarrhoea, bronchospasm, and right heart valvular disease, due to serotonin and other vasoactive substances (histamine, dopamine, hydroxytryptophan), tachykinins (kallikrein and substance P), and prostaglandins that are produced by liver metastases and released into the bloodstream without being inactivated.[39]

Gastrointestinal Stromal Tumours (GISTs)

GISTs arise either from the mesenchymal (non-epithelial) tissue of the GI tract (in the small intestine in 30-35% of cases[40]) or, rarely, from other intra-abdominal tissues.[41] These lesions represent 1-3% of all GI malignancies[42] and affect people between 40-60 years old, with a similar frequency in men and women.[43] In GIST patients, associated malignant lesions have been reported in 2.95% up to 43% of cases.[44,45] GISTs probably originate from, or have a stem cell in common with, the interstitial cell of Cajal.[46,47] GISTs may have different origins (myogenic, neural, bidirectional, or 'null phenotype') and differ from other lesions (such as leiomyomas) for the expression of the CD117 antigen,[48,49] part of the *KIT* transmembrane receptor tyrosine kinase (RTK) produced by the *KIT* proto-oncogene. The mutation of this proto-oncogene enables oncogenic signals in the cell in >80% of GISTs. However, some GISTs are *KIT* negative but may express a mutation in another RTK, the platelet-derived growth factor receptor alpha.[50,51]

Usually GISTs are sporadic lesions and do not have specific risk factors. GISTs may arise in the setting of specific tumour syndromes: familial GISTs (high-risk for developing one or more gastric or small bowel GISTs before 18-years of age); Carney's triad (association between GISTs, paraganglioma, and pulmonary chondroma occurring in young people of both sexes); Carney-Stratakis syndrome; NF1; or Recklinghausen's NF.[52] These lesions may be classified as spindle (70%), epithelioid (20%), and mixed type (10%),[53] and generally appear to arise from the muscularis propria of the bowel wall, with an intraluminal or extraluminal growth, with or without superficial ulcerations or extensive necrosis.[54] Patients may present with: bleeding into the bowel or abdominal cavity, anaemia, and abdominal pain, dyspepsia, nausea or vomiting, constipation or diarrhoea, frequent urination, and fatigue or a palpable mass. In about 25% of cases, GISTs are discovered incidentally during diagnostic imaging or surgery performed for other problems, and about 5% of GISTs are found at autopsy.[55-57]

Lymphoma

Lymphoma in the small intestine may be defined as primary when there are no peripheral or mediastinal lymphadenopathies, normal white and differential blood cell count, and no evidence of liver or spleen involvement, or it can be a component of systemic disease with GI involvement.[58] The primary intestinal lymphoma is the most common extranodal form, arising from the lymphoid aggregates in the submucosal layer; the ileum is the most common location. Risk factors for developing

small intestine lymphomas are coeliac disease, Crohn's disease, AIDS, Epstein-Barr virus infection, immunoproliferative small intestinal diseases (IPSID), long-term immunosuppressive therapy, and radiation and/or chemotherapy.[59,60] Lymphomas of the small intestine are generally divided into IPSID lymphomas, enteropathy-associated T cell lymphomas (EATLs), and other 'Western'-type non-IPSID lymphomas (e.g. diffuse large B cell lymphoma, mantle cell lymphoma, follicular lymphoma). Recently there was an increase in incidence of EATL in the US, maybe for the increasing seroprevalence of coeliac disease and better recognition of rare type of T cell lymphoma.[60] Principal symptoms in lymphomas are fever, weight loss, and drenching night sweats.[61]

Melanoma

Melanoma in the small intestine may be primary or a metastasis from a cutaneous primary lesion; sometimes it is impossible to establish whether the lesion is primary or secondary.[62] Primary intestinal melanoma is a rare carcinoma upon which different hypotheses are made of its origin, including that it is a metastasis of unknown origin.[62-68] Primary intestinal melanomas tend to be more aggressive and have a worse prognosis than cutaneous ones.[62] The neoplasia is more frequent in men, and occurs mainly in the ileum.[69,70] Metastatic intestinal melanomas are usually found in patients with a history of cutaneous, anal, or ocular melanoma; the frequency ranges from 35-70%[71-73] and may develop, either after some years from primary melanoma excision, or just 6 months after detection of a primary lesion.[67,75,76] Usually a metastatic melanoma presents with multiple polypoid masses that may be pigmented or not.[74,75] Symptoms are usually abdominal pain, intestinal obstruction, constipation, haematemesis, melena, anaemia, fatigue, weight loss, palpable abdominal mass, intestinal intussusception, and rarely, perforation.[74,77]

DIAGNOSIS

Small bowel tumours present with different and sometimes nonspecific symptoms, and a prompt diagnosis is not always so easily performed. The optimal diagnostic technique varies depending on the site and size of the tumour. In the past, the two most used diagnostic techniques were barium small bowel follow-through (SBFT) and enteroclysis; the former had a sensitivity of 30-44%[78] and was gradually abandoned for more sensitive technologies.[79] Enteroclysis utilises two different contrast techniques, thus enhancing the sensitivity up to 90%, compared to SBFT.[80] This technique can miss small lesions or lesions having continuous mucosal lining with adjacent mucosa, and causes discomfort to patients,[2] so it is now used less.

Computed tomography (CT) with the new technologies allows imaging of the entire abdomen in thin slices with lower artefacts than a conventional CT scan. Recently, CT enteroclysis plus enterography has been introduced; it permits an enhanced CT scanning and image processing after distension of the small bowel loops by using an orally administered high-volume contrast medium.[2] The combination of oral and intravenous enhancement permits a better recognition of hypervascular masses, as carcinoids or GISTs,[81,82] and enables an extraluminal visualisation, allowing a better tumour staging.[79] In a recent study, CT enterography showed an 84.7% sensitivity and 96.9% specificity in detecting tumours.[83] CT enterography has some limitations such as incomplete bowel distention, that can limit the interpretation of images in some patients because of a delayed contrast ingestion or scanning,[84] and radiation exposure.[85,86]

Magnetic resonance enterography obtains imaging similar to CT without radiation, but has some important limitations, such as higher costs, more variable image quality, and lower spatial resolution compared to CT scan,[87,88] although a recent study has shown a 95% overall diagnostic accuracy for small intestinal tumours.[89] Moreover, the technique is not always available in clinical practice.

Positron emission tomography (PET) with fluorodeoxyglucose may play a role in detecting adenocarcinomas, sarcomas, and some lymphomas, but it is not so useful for carcinoids. Recently, novel PET modalities with ^{18}F-dihydroxy-phenylalanine,[18] ^{11}C-5-hydroxytryptophan,[11] and ^{68}Ga-DOTATOC have been developed and seem to offer higher spatial resolution than conventional somatostatin-receptor scintigraphy, with improved sensitivity for detecting small lesions.[90,91]

Octreoscan™ uses a radiolabelled form of somatostatin to detect NET metastases outside the abdominopelvic region. It is also able to offer functional information regarding somatostatin receptor expression in order to predict the response to treatment.[92] Recent advances in digestive endoscopy allow an accurate diagnosis of lesions in the small intestine and, with the exclusion of capsule

endoscopy, attainment of a histology specimen or to perform therapeutic procedures. Upper GI endoscopy and colonoscopy permit identification and management of lesions proximal to ligament of Treitz or in distal ileum and rectum.[2]

Push enteroscopy (PE) enables detection of lesions until proximal jejunum because push video enteroscopes are 200-250 cm long (depending on type and manufacturer).[2,93] PE is easy to perform, the overtube is reusable, and there is no need to set up a special system (e.g. a pump control system), so procedure-related costs are low.[94] Complications occur in <1% of cases and are duodenal mucosal stripping or perforation, pancreatitis, or Mallory–Weiss tear.[93]

Double balloon enteroscopy (DBE) was introduced in 2004 and was the first therapeutic deep enteroscopy. DBE may be performed by the oral (antegrade) or aboral (retrograde) route, under different sedation on the basis of the approach. Usually it is a 'targeted procedure' in which lesions have been previously identified on prior capsule endoscopy or radiological imaging. The diagnostic yield of DBE ranges from 43-80%.[95-97] Like PE, DBE is associated to some complications (perforations, bleeding, and pancreatitis) ranging from 0.8% for diagnostic, to 4% for therapeutic procedures. Pancreatitis was reported in 0.2-0.3% of cases but its incidence appears to have decreased over time.[95] The German double-balloon registry reported a 0.005% mortality rate related to post-polypectomy perforation and subsequent post-surgical pancreatitis.[98]

Single balloon enteroscopy (SBE), introduced in 2007, has one balloon at the distal end of the overtube. The success rate of total enteroscopy ranges from 15-25%; the diagnostic yield of SBE ranges from 47-60%. The complication rate of 1% includes perforation and pancreatitis.[96]

Spiral enteroscopy (SE) by the Endo-Ease Discovery is performed using a spiral overtube made of polyvinyl chloride. The main difference between balloon-assisted enteroscopy and SE is that the latter uses a continuous pleating of the small bowel by a clockwise rotation of the overtube, rather than the push-pull technique.[79,93] Its diagnostic role has not yet been established and additional studies are necessary.[79]

Capsule endoscopy (CE) consents to obtain a direct visualisation of mucosa of the entire intestinal lumen, and is safe and less invasive than other endoscopic procedures, with a very low risk of retention. It has a high detection rate (65.8%) for small bowel tumours, compared with other radiological techniques,[99] determines the extension of tumour involvement, and assesses the response to treatment.[100] CE has some limitations too; the exact location of the lesion is difficult to establish and there are false positive or false negative findings because the capsule flows into the small intestine in absence of endoluminal insufflation. Small bowel preparation, peristalsis, or incomplete examination may also affect the diagnostic accuracy.[79]

Endoscopic ultrasonography (EUS) is the most accurate technique for distinguishing leiomyomas from other submucosal lesions because the leiomyoma arises from the muscularis propria (the fourth hypoechoic layer of the intestinal wall). EUS is able to differentiate benign from malignant lesions; features of malignancy are the disruption of tissue layers, the changes in vascularisation and tissue stiffness, and the presence of enlarged lymph nodes. EUS features have a positive predictive value of 100% for a malignant or borderline GIST. The diagnosis of GIST may be further improved by the combined use of cytologic analysis and immunohistochemistry for *KIT* mutations by EUS-guided fine needle aspiration.

TREATMENT

Adenocarcinoma

Currently, the only option available to treat small bowel adenocarcinoma with a curative intent is surgical resection. The type of resection differs, according to the location of the tumour: jejunal and ileal lesions require wide resection, removing both the mesentery and lymphatics up to the superior mesenteric vessels.[101] If tumour is located near the ileocaecal valve, the ileocolic or right colon resection is recommended. In duodenal tumours early lesion can be resected by endoscopy or push enteroscopy,[102] while surgical laparotomy or laparoscopy is required for endoscopically unreachable lesions. Lesions of proximal duodenum require pancreaticoduodenectomy, while more distant lesions can be amenable to pancreas sparing duodenectomy.[103] Relapse mostly occurs in the form of local recurrence and peritoneal carcinomatosis. There is no evidence of a significant benefit in survival with adjuvant chemotherapy after surgery, but chemotherapy is frequently used because these lesions tend to recur.[12,104]

Neoadjuvant therapy should be used for unresectable lesions and seems to improve survival; however, data are available only for a small number of patients.[105,106] Another possible targeted treatment is the use of biological agents, in particular, the vascular endothelial growth factor inhibitor bevacizumab.[107] The role of more radical resection, or metastasectomy, for advanced lesions is not clear, but some reports refer a role for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.[108,109] Palliative approaches consist of resectional or bypass procedures. In the case of obstruction by lesions accessible by endoscopy, self-expandable metal stent placement is the best option.[110] Palliative radiotherapy may have a role in duodenal tumours.

NETs

Surgical resection is usually the option for NETs of any size and should include resection of adjacent mesentery and lymph nodes. Patients with lesions near the ileocaecal valve require right hemicolectomy. Partial small bowel resection could be performed for more proximal tumours. Superficial tumours, accessible by endoscopy, may be resected endoscopically.[98,111] In metastatic liver disease, resection of hepatic metastases prolongs the disease-free survival; non-surgical ablation (cryo/alcohol/radiofrequency ablation) and hepatic transarterial embolisation (TAE) or chemoembolisation (TACE) should also be options in these cases.[5] Some patients with isolated liver metastasis may benefit from orthotopic transplantation.[112,113] Surgery is not possible in most patients with carcinoid-syndrome but a debulking surgery could give a short-term relief to patients.[5] Metastatic NETs are generally managed with the somatostatin analogues octreotide and lanreotide.[98] Octreotide can also be administered in the perioperative period to mitigate the risk of precipitating carcinoid symptoms while mobilising the tumours during surgery. Systemic traditional chemotherapy is not usually undertaken because NETs are particularly resistant.[5]

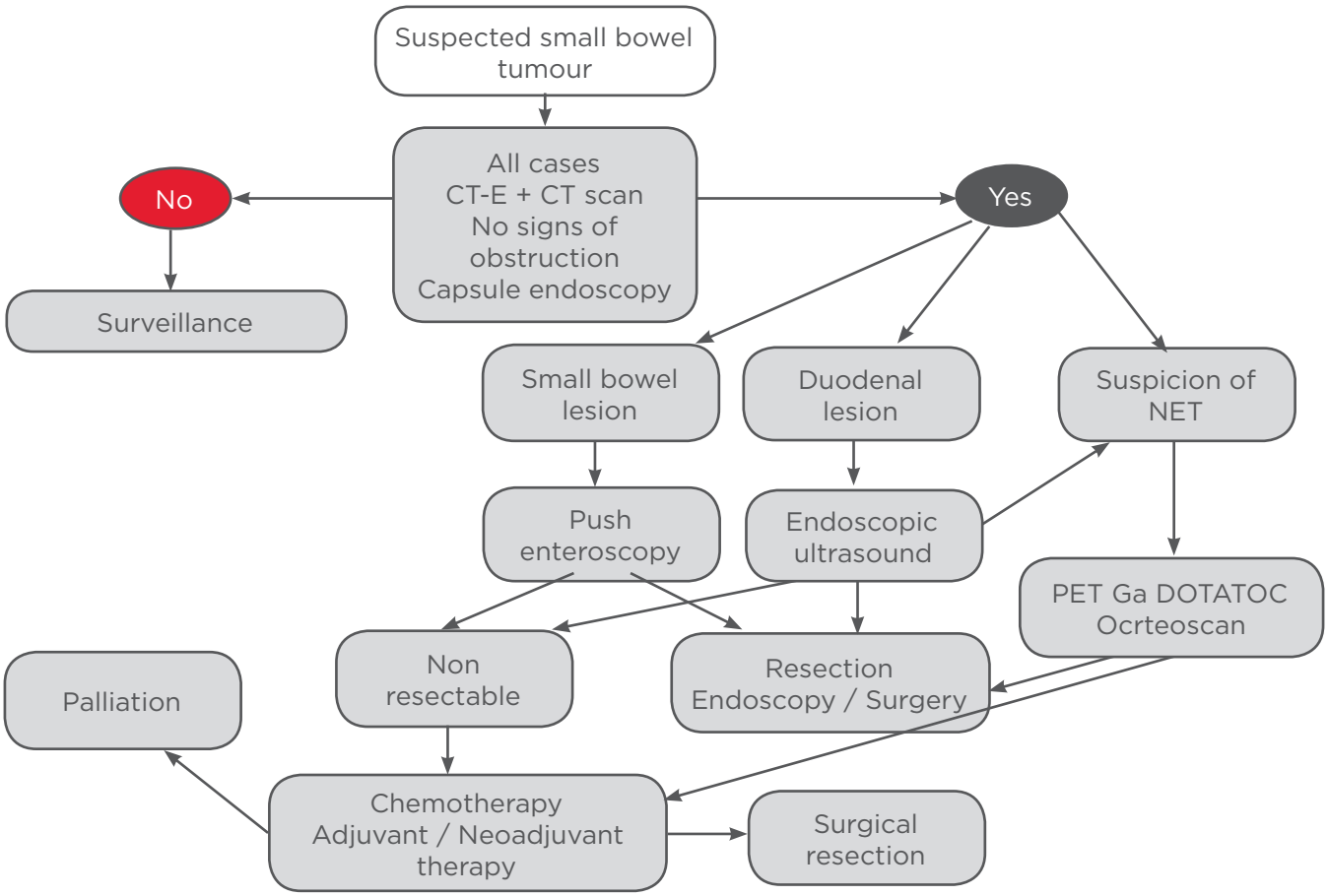

Figure 1: Simplified algorithm of diagnosis and treatment of small bowel neoplasms.
CT-E: computed tomography enterography; NET: neuroendocrine tumour; PET: positron emission tomography.

GISTs

Surgery is the treatment of choice for GISTs. Small gastric GISTs can be excised at laparoscopy;[52] local recurrence is generally due to an incomplete resection.[114] Survival after complete resection ranges from 48-80% at 5 years; in incomplete resection, only 9% of patients survive for an average of 12 months.[115,116] Patients with lesions >3 cm or with malignant metastatic disease (10-20% of cases[111,112]) can be treated with a tyrosine-kinase inhibitor, imatinib. Imatinib can also be used as neoadjuvant therapy. If the tumour becomes resistant to imatinib, it could be treated with a broader spectrum tyrosine kinase inhibitor, sutinib.[12] Surgery is not recommended for GIST progressing at several sites, except to relieve severe symptoms such as bowel obstruction or bleeding.[52] In patients with metastatic disease, radiotherapy is used to control abdominal metastases and relieve symptoms,[113] while palliation is done by hepatic TAE or TACE, and radiofrequency ablation.[117-119]

Lymphoma

The gold standard in treatment of lymphoma is chemotherapy. Resection should be an option in case of bleeding, obstruction, or perforation.[120] In patients with Helicobacter pylori or Campylobacter jejuni infection, the eradication of the infection results in regression of early stage immunoproliferative small intestinal disease; however, most patients relapse with high-grade disease. In these cases, radiotherapy and chemotherapy are the mainstay of treatment.[121-123] EATL is treated with combination chemotherapy using anthracyclines such as epirubicin.[12]

Melanoma

Primary intestinal metastatic melanoma requires surgery.[124] Metastasectomy should be done in patients for whom complete removal of lesions is not possible because in these cases, surgery is the only palliative therapy.[66] Chemotherapy, immunotherapy, and biochemotherapy are included in the treatment of metastatic disease as adjuvant and neoadjuvant treatment.[24,125]

An algorithm of diagnosis and treatment of small bowel neoplasms is reported in Figure 1.

CONCLUSIONS

Small bowel tumours include a large group of lesions with increasing incidence, particularly for NETs. Unfortunately, given the absence or non-specificity of symptoms, the majority of lesions are diagnosed late and have a poor prognosis. In recent years, diagnostic technology and new therapies have led to improved life expectancy. A better understanding of the aetiopathogenesis and risk factors will very likely result in earlier diagnosis and a more effective treatment of these tumours.

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THE GEOGRAPHIC VARIANCE OF *HELICOBACTER PYLORI* INFECTION IN EUROPE AND ITS IMPACT ON THE INCIDENCE OF GASTRIC CANCER

***Ayse Nilüfer Özaydın**

Department of Public Health, Medical Faculty, Marmara University, Istanbul, Turkey
**Correspondence to nozaydin@gmail.com*

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ABSTRACT

The discovery of *Helicobacter pylori* was hopeful as this agent was included in the list of 'preventable-infectious carcinogens', and many non-treatable gastroduodenal disorders with uncertain causes became treatable infectious diseases. Nevertheless, nowadays frequent antibiotic resistance is observed among *H. pylori* infections, sometimes as high as 95%. *H. pylori* is a bacteria that existed for a very long time, which was only recognised in the last 30 years. It can cause a variety of symptoms leading to gastroduodenal disorders from chronic inflammation in the gastrointestinal system to non-cardia gastric cancer. It is acquired in the early years of life and infection is commonly lifelong. The accepted primary route of transmission is person-to-person contact because humans are the only known significant reservoir of *H. pylori.* The target cell of *H. pylori* is the gastric mucus secreting cell. The prevalence in Europe shows a huge variety with almost all studies showing a decreasing trend. During childhood the highest prevalence was from Turkey (56.6%) and the lowest was from Czech Republic (4.8%). Among adults, the overall prevalence was found to be between 18.3% (Denmark) and 82.5% (Turkey), with substantial country-to-country variations. The prevalence rate differs by socioeconomic lifestyle characteristics and also genomic structure; it is also higher in less developed countries/populations. While the more commonly used test to determine *H. pylori* infection is serology, immunoglobulin G by enzyme-linked immunosorbent assay, the urea breath test (UBT), and stool antigen testing are non-invasive tests which are also recommended.

Keywords: Prevalence, childhood, adulthood, European countries, gender, alcohol consumption.

INTRODUCTION

At the beginning of the 1990s *Helicobacter pylori* was placed in the potential human carcinogen list by International Agency for Research on Cancer because of a causal link showing it to cause non-cardia gastric carcinoma.[1] It is estimated that the cancer cases caused by infectious agents amount to 20% in total. Among these agents, the highest proportion belongs to *H. pylori* with 37% of the causes (Figure 1).[2] The cancer frequency is consistently increasing throughout the world. The ratio of cancers caused by infectious agents is estimated to be around 23% in developing countries, whereas this ratio is close to 7% in developed countries. If these cancer-causing infectious agents can be controlled or treated, 26% of cancer cases in developing countries and 8% in developed countries can be prevented.[1,3]

H. pylori was described by Barry Marshall and Robin Warren with the successful isolation and culture.[4,5] *H. pylori* can colonise the human stomach and induce inflammation of the gastric mucosa.[6] It is accepted that *H. pylori* can cause chronic gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer.[7] *H. pylori* as an infectious agent has been claimed to be acquired during childhood, stay in latency for long periods of time, and cause gastric diseases in advanced adult ages. Where the morbidity rate of *H. pylori* is high, the mortality rate is low.[8] *H. pylori*

infections can be diagnosed by a variety of tests and usually treated with antibiotic use.[9] However, recent increase in antibiotic resistance among *H. pylori* is starting to affect the successful treatment, and preventive vaccinations still do not exist.[6] Even with the increasing attention to *H. pylori*, the transmission route, acquisition, and loss of *H. pylori* are not understood completely.[8,10] The prevalence of *H. pylori* in the developing world is widespread even though a decreasing trend is observed in developed Western countries. This review is going to focus on the prevalence of *H. pylori* infection in childhood and adulthood periods in Europe, with the aim of aiding the understanding of infection and related risk factors, through the basic information available to the writer and with the main interest on large scale, population-based studies since 2000.

Characteristics of *H. pylori*

H. pylori is a highly heterogeneous bacterium showing a large genomic diversity.[1] Humans with multiple strains have been observed, and during colonisation of a single host, the bacterium can genotypically and phenotypically change.[11] *H. pylori* genotypes were found to be diverse in different geographic areas, especially cagA and vacA. Strains from Western countries predominantly possessed cagA Type 2a, vacA s1a or s1b/m1a, or vacA m2a genotypes, whereas strains from East Asia possessed cagA Type 1a, vacA s1c/m1b, or vacA m2b genotypes. Studies from Turkey, which has the highest *H. pylori* prevalence, showed that Turkish strains predominantly possessed cagA Type 2a, vacA s1a/m1a, or vacA m2a genotypes, which were typical genotypes in strains from Western countries.[12] The presence of duodenal ulcer and gastric cancer were found significantly related with *H. pylori* vacA s1a, cagA, and cagE genotypes. On the other hand, cagE and vacA s1a genotypes are independent predictors of duodenal ulcer, and babA2 and cagE genotypes are independent predictors of gastric cancer.[13] Production of immunoglobulin A (IgA) antibodies has also been associated with a CagA-positive infection, which is associated, in turn, with an increased risk of severe complications, such as gastric cancer. In a study of Finnish adults, maturation of the IgA response in *H. pylori* infection in adulthood (both as an increased number of IgA responders and in rising antibody titres) was presented, whereas the IgG titres in children have disappeared in adulthood.[14]

H. PYLORI PREVALENCE AND GEOGRAPHIC DISTRIBUTION

Predominantly, the recent population-based and large scale studies were taken into consideration for this review. This was not an easy task, mainly because they cannot be compared in reality as they are so different from each other; for example study types, study populations, selection methods of sampling, and also tests used to define the *H. pylori* status. Several non-invasive *H. pylori* tests are established in clinical routine.[9] The Maastricht IV/Florence Consensus report declared that the urea breath test (UBT) using 13C urea remains the best test to diagnose *H. pylori* infection, has a high accuracy, and is easy to perform. Stool antigen test is regarded as an equivalent to the UBT and, from a diagnostic accuracy standpoint, a monoclonal test from a validated laboratory is used.

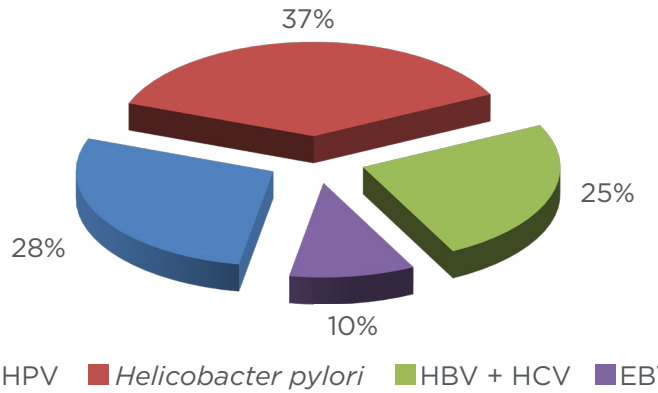

Figure 1: Cancers due to five infectious agents (correspond to 18.6% of total cancer incidence).[2]
HPV: human papilloma virus; HBV: hepatitis B virus; HCV: hepatitis C virus; EBV: Epstein–Barr virus.

Table 1: The prevalence of *Helicobacter pylori* in childhood, in various countries, after 2000.

H. pylori (+)%	n	Average age/ Age groups (years)	Diagnostic Test	Study population	Country	Reference
31.6	844	0-15	Stool test	Asymptomatic children	Portugal	Oleastro et al.[16]
15.8	284	1-14	Stool test	Descriptive	Spain	Leandro Liberato et al.[17]
9: 2005/2006 9: 1993 19: 1978	545	7-9 6-8	Serology	Birth cohort study	Netherlands	Den Hoed et al.[18]
1.2 0.5 (Dutch parents) 2.6 (non-Dutch parents)	1,258	2-4	Serology	A serum bank of 6,127 children who attended the community child healthcare centres in the Dutch province of Zuid-Holland.	Netherlands	Mourad-Baas et al.[19]
6.5: 2006 5.7: 2000 6.1: 1998	1,905	School children School starters-8th Grade students	UBT	Long-term, follow-up study	Germany (Leipzig)	Bauer et al.[20]
27	137	1-4	Stool assay	1 year follow-up of asymptomatic Turkish children on whom participating pediatricians had performed routine health screening Sept. 1997-Oct. 1998	Germany	Rothenbacher et al.[21]
4.8 (≤15 years)	1,837	5-98	UBT*	General population (22 cities)	Czech Republic	Bures et al.[22]
7.1	1,545	0-15	Stool test	Cross-sectional	Czech Republic	Sykora et al.[23]
56.6: 2004 49.5: 1998 14%: incidence rate 5.5%: loss rate	327	3-12 13.5 mean age	UBT	Cohort of healthy school children	Turkey	Özen et al.[24]
66.3: 2000 78.5: 1990	219 184	7-14	Serology	Cohort of primary school, healthy children	Turkey (Ankara)	Ozden et al.[25]
43.9 Father: 76.3 Mother: 85.4	346	Children	Serology	Descriptive healthy children	Turkey (Eastern Turkey)	Yılmaz et al.[26]
13: 2005 44: 1995	370 307	2-19	Serology	Cross-sectional	Russia (St Petersburg)	Tkachenko et al.[27]
28.1 42.2	296: 2002 425: 1991	Children	Serology	Hospital based	Estonia	Oona et al.[28]

*The cut-off point was 3.5 for urea breath test (UBT) test.

Table 2: *Helicobacter pylori* prevalence in adults according to various European countries after 2000.

H. pylori (+)%	n	Average age/ Age groups (years)	Test	Study population	Country	Reference
71.3	430	Adults	Serology	Hospital based controls	Spain	Sanjose et al.[29]
40.0	407	49-51	Serology	The birth cohort	UK	Pearce et al.[30]
2	3,928	50-59	UBT	Cross-sectional	UK	Ford et al.[31]
15.5	10,537	20-59	UBT	Cross-sectional	UK	Lane et al.[32,33]
14	10,118	1-84	Serology	Cross-sectional	UK	Vyse et al.[34]
27.5	8,455	40-49	UBT	Randomised clinical trial	UK	Moavyedi et al.[35]
37.7	22,612	All age group	Gastric biopsy	In medical centre	Belgium	Miendje[36]
15.2: 2007 36.2: 1988	11,238	Adults	Gastric biopsy	Western European patients		
40.0: 2007 71.7: 1988	3,200	Adults	Gastric biopsy	North African patients		
18.3: 2009 20.1: 2003	36,629	42 median age 26-56	UBT	Primary health care level	Denmark	Dahlerup et al.[37]
17.5 (Eradication rate 95%)	20,000	40-65	Serology + UBT	Randomised clinical trial	Denmark	Christensen et al.[38]
24.7	2,527	Adults	Serology	Population based study	Denmark	Rosenstock et al.[39]
35.0	117	16-40 30.9	Serology	Nested case control	Sweden	Persson et al.[40]
40.0	499	51-79 69	Serology	Case-control	Sweden	Yee et al.[41]
25	1,030	17-79 50.5	Serology	Cross-sectional	Sweden	Sörberg et al.[42]
79.2	3,564	17-99 54 median age	Serology	Cross-sectional, General population	Latvia	Leja et al.[43]
51.9	9,953	63 '50-74'	Serology	Population based	Germany	Schöttker et al.[44]
44.4	2,318	0-30	Serology	Hospital based, Patients	Germany	Wex et al.[45]
40.7	6,545	18-79	Serology	Cross-sectional	Germany	Kuepper-Nybelen et al.[46]
23.5 39.8: ≥55 years	1,837	5-98	UBT*	General population (22 cities)	Czech Republic	Bures et al.[47]
41.7	2,509	5-100	UBT	Cross-sectional, 19 GP centre	Czech Republic	Bures et al.[48]
35	1,838	≥18	UBT*	Workplace	Slovak Republic	Kuzela et al.[49]
63.8 M:73.5/ FM:63.8	960	18-60 36.8	Serology	Employees in a company	Romania	Sporea et al.[50]
82.5	4,622	≥18	UBT	Cross-sectional	Turkey	Ozaydin et al.[15]
63	200	21.4	Stool test	Descriptive	Turkey	Yucel T et al.[51]

UBT: urea breath test; GP: general practitioner.

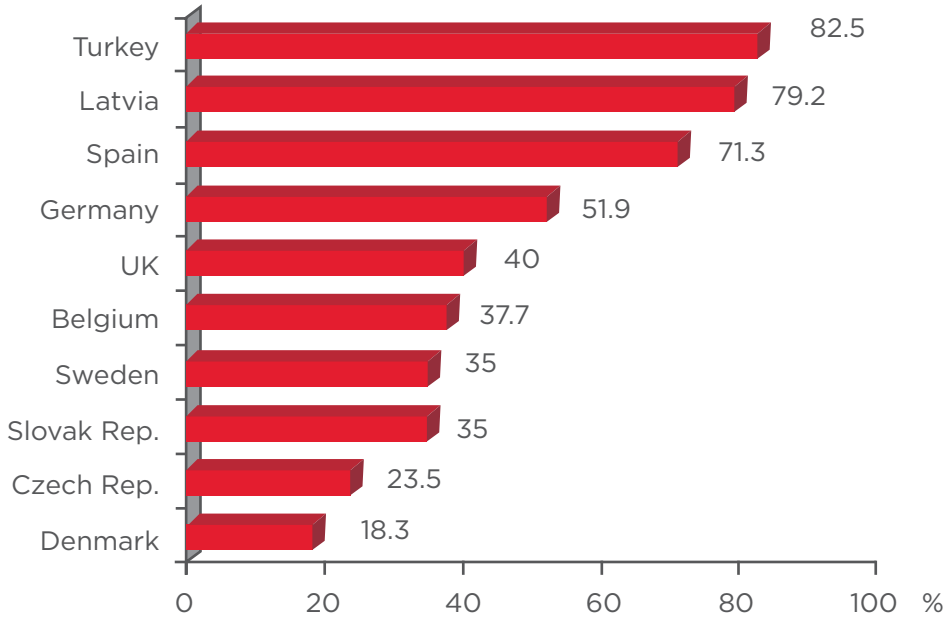

Figure 2: The prevalence of *Helicobacter pylori* in adults in Europe after 2000 according to various countries (the latest results from published literature were presented in the graph).

The third commonly used method to diagnose *H. pylori* infection is serology and, given the chronic status of the infection, IgG detection by enzyme-linked immunosorbent assay is favoured. Another problem that must be mentioned is the relative lack of large scale, population-based, representative, cross-sectional studies. One of the population-based, representative studies was done by Ozaydin et al.,[15] where the sample was selected throughout the country. All related studies listed in this review, in Tables 1 and 2 were published about European countries after 2000, considering the frequency of *H. pylori* infection in childhood and adulthood.[15-51]

European Prevalence of *H. pylori* in Childhood

In Europe, after 2000, as far as the author can reach, there were few large scale studies about *H. pylori* prevalence in childhood (Table 1). Among the present studies, according to the latest one from each country, the highest prevalence was found in Turkey[24] (56.6% among 3-12 years), the lowest seroprevalence rate was from Czech Republic[22] with 4.8% ≤15 years. However, there was a huge range between the prevalence of countries in Europe, with almost all of them showing a decreasing trend.[16-28]

European Prevalence of *H. pylori* in Adulthood

A great diversity of *H. pylori* infection prevalence among adults in Europe has been recorded since 2000, with an overall prevalence for adulthood being between 18.3-82.5%, with substantial country-to-country variations (according to the latest literature from each country; Table 2, Figure 2).[15,21-51] The highest prevalence of 82.5%, for adults aged ≥18 years was measured by the UBT test in Turkey, by a population-based, nationally representative, cross-sectional study (n=4,622),[15] whereas the lowest prevalence of *H. pylori* was found in Denmark, by UBT test, as 18.3%, at the primary healthcare level.[33]

The Role of Family Members in the Acquisition of *H. pylori* Infection

H. pylori infection is acquired usually after the first year of life and persists, at least, for decades.[1,8,42] Under the conditions of poor hygiene, gastrointestinal microbes have been easily transmitted. Still, such enteric transmission occurs in some developing countries as *H. pylori* are ubiquitous, and their presence is possibly nearly universal. Oral-oral, faecal-oral, waterborne, and iatrogenic routes are usually accepted ways of transmission of *H. pylori*. Because humans are the only known significant reservoir, intra-familiar clustering, person-to-person transmission, appears to be the predominant mode of transmission.[1,4] Risk factors for *H. pylori* transmission can be listed such as crowded family, parents (especially mothers) with *H. pylori*, *H. pylori*-positive older siblings, and household crowding during childhood. In Sweden,

Kivi et al.[52] studied *Helicobacter* status in family members as risk factors for infection in children, and showed that *H. pylori* infections in mothers and siblings in high prevalence countries stand out as strong factors for infection risk, although birth in high prevalence countries was an independent risk factor. The role of infected parents with *H. pylori* infection was also studied; an infected mother is shown to be a much stronger risk factor for childhood infection than an infected father.[21,53] The evidence about infected parents showed that mothers especially may play a key role in the transmission of *H. pylori* to the children.[21,53] It was found that sibling number in the household was independently associated with prevalence of *H. pylori* infection; whereas prevalence of infection in those with no siblings was 20%, it was 63% with eight or more siblings.[31]

Reasons behind the Inter-Country Variation

Different *H. pylori* subtypes in different countries

It is known that a clear phylogeographic differentiation exists between *H. pylori* strains from different geographic areas to an extent that it is possible to use these strains as a marker of the origins of various ethnic populations.[12,13,54] The virulence gene cagA, and vacA genotypes in particular, differ in different geographic areas, and are commonly used as markers. However, the difference between strains is not sufficient to explain the difference of prevalence between the countries in Europe.

Significant sociodemographic differences

Low prevalence rates in developed countries, high prevalence rates in developing countries, and even prevalence rate differences between regions in the same countries, are reported based on the different sociodemographic and socioeconomic levels (Tables 1 and 2, and Figure 2).

The effect of birth cohorts

The prevalence rate is decreasing with each new year, but this decrease is not parallel in different countries. Highly organised population-based screening projects were implemented in a small number of European countries, and antibiotic treatment was administered to the small number of positives in these screening projects.[32,33,35,38] This was not advised by their researchers, even with the indication number being too high, as the dyspepsia treatment and overall life quality improvement was negligible. However, during these screening projects, positives were administered antibiotics and 95% of the *H. pylori* infections were eradicated. If the fact that the only host of *H. pylori* is humans is taken into account, this might be accounted for as a very important intervention to the chain of infection.

Antibiotic resistance

After identification by Warren and Marshal, *H. pylori* was supposed to be eradicated by antibiotics easily. However, until the present time, the prevalence of *H. pylori* gradually decreased, yet infection is still common in some countries.[15] Two antibiotics (amoxicillin and clarithromycin) plus a proton pump inhibitor, given for 1 or 2 weeks, has been recommended as the treatment of *H. pylori*.[6,9,55] However, failure of this treatment was reported due to antibiotic resistance. Clarithromycin, metronidazole, tetracycline, fluoroquinolones, and rifampicin resistance has recently become an emerging issue. Although the prevalence of antimicrobial resistance shows variation even among regions per antibiotic, antibiotic resistance in *H. pylori* is widespread, and it can be as high as 95% in some cases. For example, metronidazole resistance is around 35% in developed countries, yet it varies between 20-95% in developing countries. For example, *H. pylori* prevalence is very high in Turkey, and 27.5-40.5% resistance to clarithromycin and up to 85% resistance to metronidazole has been reported.[56,57]

The causes of resistance are not known exactly, but widespread consumption of antibiotics could be one of the reasons. Also, there might be some factors related with antibiotics unknowingly consumed with food. Antibiotics are widely used in pasture animals and recently about 80% of antibiotics produced in the US are given to farm animals for enhanced growth.[58] In addition, usage of recombinant bovine growth hormone is a known side-cause of mastitis, and widespread antibiotic treatment for mastitis is known in milk production.[59] It is hypothesised that this side consumption of antibiotics may contribute to emerging antibiotic resistance.

Alcohol consumption variations

In a study done in the UK by Murray et al.[60] in 2002, higher wine consumption was found to lower *H. pylori* risk by 11%, and a similar effect was confirmed for beer consumption. In 2005, Kuepper-Nybelen

et al.[61] reported that alcohol consumption may facilitate elimination of *H. pylori* infection among adults, and a similar trend is reported by Ozaydin et al.[15] in 2013, in Turkey. Alcohol consumption was reported to be 7.4% in male Turkish adults, and subsequently *H. pylori* risk is found to be 2.18-times higher in adult males who never drink alcohol. However, alcohol and tobacco use for women are not found to be related to *H. pylori* infection risk, maybe because alcohol and tobacco use were so low in Turkish women (1%).[15] Interestingly, in countries with high *H. pylori* infection, the consumed alcohol amounts are low, whereas in communities with low and decreasing *H. pylori* prevalence rates, alcohol consumption is high and increasing. This might have contributed to the decrease in *H. pylori* prevalence.

Citrus fruit consumption

An interesting result was found in Turkey; people in the South of Turkey have the least *H. pylori* prevalence, whereas the Western region is more developed, have better housing conditions, and smaller family size. In the Southern region of Turkey, oranges, lemons, tangerines, and bitter oranges are produced. People eat them or drink their fresh juices all year round because they are cheap and plentiful. *H. pylori* may not survive in acidic gastric conditions produced by the acidic citrus fruits.[15,62,63]

CONCLUSION

H. pylori are unique bacteria that are known to cause cancer, yet our knowledge and understanding of this organism is far from complete, or even satisfactory. Modes of transmission are all studied extensively, but the evidence remains rare and uncertain. According to the present evidence, the prevalence of *H. pylori* infection in Europe shows a huge variety, with almost all studies showing a decreasing trend. The genomic structure of *H. pylori* has been reported from different geographic regions; strains from Western countries, which have lower incidences of gastric cancer, predominantly possessed cagA Type 2a, vacA s1a or s1b/m1a, or vacA m2a genotypes, whereas strains from East Asia, which has a higher incidence of gastric cancer, possessed cagA Type 1a, vacA s1c/m1b, or vacA m2b genotypes. As is the case with many gastrointestinal system infectious agents, many choices exist for treatment, yet most of these treatment approaches for *H. pylori* have a 20% failure rate, as well as emerging antibiotic resistance. Under the light of these points, research on knowing this organism from a better standpoint, the roots of transmission, and even on the survival of this bacteria is elemental, as this new understanding may be employed to explain and comprehend the differences in prevalence of infection and incidence of gastric cancer between different regions and communities.

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MANAGING COMPLICATED DIVERTICULAR DISEASE IN 2014

Marek Soltes,[1] Dorin Popa,[2] *Abe Fingerhut,[3] Chadli Dziri[4]

1. First Department of Surgery, University of Pavol Jozef Šafárik, Košice, Slovakia
2. Department of Surgery, University of Medicine and Pharmacy "Carol Davila", University Emergency Hospital, Bucharest, Romania
3. Section for Surgical Research, Department of Surgery, Medical University of Graz, Graz, Austria
4. Department B of General Surgery, Charles Nicolle Hospital, University of Tunis El Manar, Tunis, Tunisia
**Correspondence to abefingerhut@aol.fr*

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ABSTRACT

Complicated diverticular disease refers to patients who present with abscess, peritonitis, bleeding, fistula, or bowel obstruction. Management paradigms for these complications have changed enormously in the last 20 years. Surgical options include primary resection with or without anastomosis, exteriorisation of the perforation as the site of diversion, and more and more in recent years, simple lavage and drainage. The different classifications, the indications and techniques of interventional radiology, and endoscopy, as well as other minimally invasive or traditional surgical treatment of these complications are covered in this review.

Keywords: Diverticular disease, complicated diverticular disease, abscess, peritonitis, primary resection, primary anastomosis, colostomy, Hartmann procedure, lavage, drainage.

INTRODUCTION

Diverticular disease (DD) may be defined as the presence of diverticula, in fact, pseudodiverticulosis,[1,2] saclike mucosal outpouchings that protrude the colon through the muscular layer; when inflammation ensues (microperforations), the inflamed diverticula (called 'diverticulitis') can subside, either spontaneously or with minimal medical treatment, or become 'complicated' (approximately one-fourth of patients), characterised by an intensive inflammatory infiltrate with macrophages. 'Complicated' DD refers to patients who present with abscess, peritonitis, bleeding, fistula, or bowel obstruction.

Whether an inflamed diverticula proceeds toward a more serious complication or not depends on the magnitude of the (micro or macro) perforation, the amount, nature, and location of spillage of intestinal contents, and the local mechanisms with which the body defences react. According to a recent review,[3] 15-20% of diverticulitis cases develop complications.[1,2] Abscesses are in fact considered as the result of microperforation and/or walled-off micro or macroperforations. Infection can also spread locally to neighbouring structures such as the ovary, the scrotum, or even the hip joint, or travel via the portal vein to cause pylephlebitis and, ultimately, hepatic abscess formation. Uncontained perforations result in peritonitis, classically subdivided into purulent and faecal peritonitis. Obstruction can be caused by pseudotumoural formation of the colonic wall, compression from abscess, inflammatory adhesions to nearby bowel, responsible for early obstruction, or more rarely, strictures or bands created by any of the above, leading to progressive fibrosis and late obstruction. Fistulas most commonly involve the bladder,[4] but also include colovaginal (typically in the hysterectomised woman),[5] coloenteric, and colocutaneous fistulas. Management paradigms for complications, such as localised abscess, generalised peritonitis, and bleeding, have changed enormously in the last 20 years; interventional

radiology, endoscopy, as well as other minimally invasive treatments of these complications, form the basis for this review.

COMPLICATIONS AND CLASSIFICATIONS

Several classifications have been developed to describe and guide the management of the range of complications in DD. One of the best known and most widely used was published in Canada by Hinchey in 1978[6] (Table 1). Based on progressively increasing degrees of infective complications, found intraoperatively, the Hinchey classification does not take into account any preoperative information (no sonography or computed tomography [CT] findings), and cannot be used in the absence of interventional or surgical therapy, which limits its use today and has led to several modifications.[2,7,8,9,10,11]

Wasvary et al.[11] added a Stage 0 in order to define uncomplicated DD and subdivided Hinchey 1 into confined pericolic inflammation or phlegmon and colonic wall thickening with pericolic soft tissue modifications (Stage 1A), different from pericolic or mesocolic disease abscess. Sher et al.[10] modified Hinchey's Stage 2 (deep pelvic abscess) to individualise distant abscesses amenable to percutaneous drainage (2a) from complex abscesses associated with fistula (2b), usually requiring surgery. The European Association for Endoscopic Surgery consensus conference[2] introduced complications other than perforation, including bleeding, strictures, fistula with other organs, and obstruction. Ambrosetti et al.[7] and Kaiser et al.[9] used CT scan to provide more precise preoperative evaluation and to scale severity.

Table 1: Stages of complicated diverticular disease.

Stage	Classification
1	Phlegmon, pericolic, or mesenteric abscess
2	Diverticulitis with walled-off pelvic abscess
3	Diverticulitis with generalised purulent peritonitis
4	Diverticulitis with generalised faecal peritonitis

According to Hinchey et al.[6]

Finally, in view of the modern concepts in therapy, Klarenbeck et al.,[12] in a complex but complete classification combining clinical, radiological, and treatment characteristics, propose to divide DD into three categories: Stage A is uncomplicated DD, Stage B, chronic complicated disease, and Stage C, acute complicated disease. While the diversity of classifications reflects the need to include either other preoperative diagnostic modalities (Hinchey's classification was intraoperative) or therapeutic modalities (not all require surgical intervention), it is difficult to recommend any one classification. The Hinchey classification is certainly the most well-known and is still used extensively. The Wasvery et al.[11] and Sher et al.[10] modifications warrant consideration for their sub-classifications of Hinchey 1 and 2. The Ambrosetti et al.[7] classification is radiologic only. Ideally the Klarenbeck et al.[12] classfication would be the best to combine clinical, radiological, and operative findings but it has not yet been met with universal use.

COMPLICATIONS AND MANAGEMENT

Although almost all international guidelines recommend antibiotic therapy for acute uncomplicated diverticulitis, (inflammation) either alone or combined with anti-inflammatory drugs, bed rest, and hygienic measures,[13,14] a recent Cochrane review[15] and a systematic review[16] found that the best available data do not support use of antibiotics in this setting. Probiotics and anti-inflammatory drugs also have their proponents.[3] The management of complicated DD varies with the type of complication (infection, perforation, bleeding, or obstruction), patient status, and local surgical expertise.

Treatment of diverticular abscesses (Hinchey Grades 1, 2) depends on the size of the abscess. Abscesses <4 cm can most often be treated with antibiotics alone, under strict clinical observation, while those >4 cm are best managed by percutaneous drainage,[17-19] usually combined with antibiotics. Drains should be flushed several times daily and may be discontinued after a radiological control or when purulent production has ceased. However, percutaneous drainage is not always successful[19] – up to 81% success rate (95% CI: 73.7-89.1)[20] – and the level of evidence and grade of recommendations[21] for this therapeutic modality is not high (Grade C).[19] In cases of continuing purulent production or suspicion of faecal content in the drain, injection of contrast

material through the drain is recommended. Intestinal fistula or drainage failures (persistent drainage) should be dealt with surgically (Grade of recommendation C).[3,22]

Surgical Management

Several options are open to the surgeon undertaking surgical management: primary resection with or without (colostomy) anastomosis, exteriorisation of the perforation as the site of diversion, and in recent years, simple lavage and drainage. The best treatment for generalised peritonitis by perforation has been debated for years. Classically, anastomosis was not advised in peritonitis and the Hartmann procedure (HP; colectomy with proximal end stoma and distal stump closure) was the procedure of choice.

Before the laparoscopic era, two randomised trials had compared primary anastomosis (PA) with HP and can be seen as precursors to damage control surgery in this setting. Kronberg et al.[23] conducted a small prospective randomised trial (62 patients) with diffuse peritonitis from perforated left colonic diverticulitis, comparing acute transverse colostomy, suture, and omental covering of a visible perforation with acute resection without PA, and concluded that suture and transverse colostomy was superior to resection for purulent (Hinchey 3) peritonitis because of lower postoperative mortality rate. Zeitoun et al.[24] and the French ARC study[24] included 105 patients in their randomised trial, comparing primary or secondary resection, and came to quite different conclusions. These authors concluded that primary resection was superior to secondary resection in the treatment of generalised peritonitis complicating sigmoid diverticulitis because of significantly less postoperative peritonitis, fewer reoperations, and shorter hospital stay.

Constantinides et al.[25] compared PA and anastomosis with and without defunctioning stoma to HP in patients presenting with Hinchey Stage 3-4, perforated diverticulitis, looking at quality-adjusted life-years gained from each strategy; they concluded that PA with defunctioning stoma might be the optimal strategy for selected patients with diverticular peritonitis - a good compromise between postoperative adverse events, long-term quality of life (QoL), and risk of permanent stoma (in 27% of HP and in 8% of PA). Several population-based studies[26] and systematic reviews[27] have found that PA with anastomosis had a statistically significant advantage over HP in terms of mortality and postoperative duration of hospital stay. However, because of the heterogeneity of the literature on the topic, they cautioned against any strong conclusions in this direction, calling for further randomised controlled trials (RCTs). Moore et al.[28] also reviewed the literature on the same topic and found that, in spite of the high morbidity and permanent stoma rate after HP, and the promotion by colorectal surgeons to perform PA, this operation continued to have a high mortality (10-15%). Two RCTs compared PA with HP. One, a European multicentre study,[29] showed that PA was better than HP, mainly because of lesser morbidity in re-establishing intestinal continuity. The other was stopped prematurely because of insufficient referrals, so no conclusions can be drawn.[30]

Surgical management of complicated diverticulitis (perforation) certainly has undergone profound modifications in the last two decades, essentially by raising the number of flares before surgery[31] (not the topic herein) and the advent of laparoscopic surgery, leading first to the possibility of colonic resection followed or not (Hartmann's procedure) by restoration of intestinal continuity, with less morbidity and mortality;[12-32] and second, to proposing simple laparoscopic lavage for peritonitis, and not necessarily followed by resection.[33,34] Heralded by the late Gerry O'Sullivan and his group from Dublin,[33,34] laparoscopic lavage without resection has taken the spotlight. Several systematic reviews[35,36] concluded that, while the laparoscopic approach with simple lavage appears feasible, the indications for simple lavage and drainage should be limited to haemodynamically stable patients with generalised peritonitis. At least four randomised trials started in the past years to compare laparoscopic lavage without resection for generalised peritonitis originating from perforation: the LAPLAND (Ireland)[37] trial, the LADIES (the Netherlands)[38] trial, and the DILALA (Scandinavia)[39] and SCANDIV trials.[40] The LADIES study was stopped prematurely, both the LAPLAND and the two Scandinavian studies are planned to terminate in 2014;[39,40] the results have not been published to date.

Faeculent peritonitis is a traditional indication for Hartmann's procedure, but reports of primary resection followed by anastomosis, with or without diversion, are accumulating even in this indication.[27-29] However, there are accumulating data[3,28] that the surgical treatment of acute

perforated diverticulitis may be performed laparoscopically (Hartmann's procedure[40] and primary anastomosis).[38] Peritoneal lavage and drainage is a non-invasive alternative, in case of Hinchey Stage 3 (purulent peritonitis) (level of evidence 3), while resection of the sigmoid (laparoscopically) is recommended for Hinchey Stage 4 (faecal peritonitis) (level of evidence 3). While one multicentre RCT seems to indicate that PA is better than HP,[29] the latter is still widely practiced, especially in faeculent peritonitis. Of note, simple fluid collections or pneumoperitoneum can be managed conservatively in haemodynamically stable patients.[41]

OTHER COMPLICATIONS

Haemorrhage

DD remains one of the most common causes of massive lower gastrointestinal bleeding, accounting for 30–50% of cases, enhanced by non-steroidal anti-inflammatory drugs in nearly 50% of patients. Bleeding from DD is usually painless, of sudden onset, and can require either transfusion or operation in up to one-third of patients.[42] About three cases out of four are self-limiting, but recurrence of bleeding occurs frequently. Ideally, the exact site of bleeding should be located to propose minimally invasive therapy (endoscopic or embolisation)[43-45] without having to resort to surgery and resection. Diagnosis can be made with nuclear scintigraphy, angiography coupled with interventional radiology, and/or colonoscopy. Sensitivity is highest for nuclear scintigraphy but only interventional radiology and/or colonoscopy can be therapeutic. 99m technetium-labelled sulphur colloid radioisotope scanning can detect bleeding rates as low as 0.1 mL/min. Another advantage is that this scan can be repeated within 24–36 hours. Emergency angiography and/or colonoscopy constitute the first-line diagnostic/treatment options. Selective emergency angiography can detect bleeding only when the bleeding rate is at least 1.0–1.3 mL/min; interventional haemostatic therapy includes injection of vasopressin and/or somatostatin (successful in >90% of cases). Embolisation for diverticular bleeding can be successful in 85-96% of patients.[43-45] Of note, however, the risk of post-embolisation ischaemia exists and can be fatal.[45]

Colonoscopy performs best when bleeding is minor or has stopped, usually within 12–24 hours after bleeding has ceased. Additionally, colonoscopy can help exclude neoplasms and carcinoma as the source of bleeding (one-third and one-fourth of cases, respectively).[13] Emergency therapeutic colonoscopy consists of local injection of epinephrine, sclerosant, or thermo-coagulation; colonoscopy allows landmarking the neoplasm by tattooing in view of future surgery. Recent endoscopic techniques include haemostatic clipping and rubber band ligation.[45] Surgery should be considered to treat bleeding either after successful but recurrent bleeding (after one or more of the above mentioned methods) or as an urgent procedure. Successful definitive surgery for diverticulum-related bleeding is directly related to whether the site of bleeding has been found. In most cases, however, surgery is performed as a last resort when the surgeon is faced with haemodynamic instability, unresponsiveness to conventional resuscitation techniques, necessity of massive transfusion, and recurrent substantial haemorrhage. Most often, however, precise localisation of the exact bleeding source is difficult. Thus, emergency surgery for diverticular bleeding often results in (blind) resection. As a consequence, recurrence is frequent and can lead to repeated operations and, not infrequently, total or near total colectomy.

Obstruction

Obstruction can be acute (inflammation) or chronic, usually due to pseudotumoural formation. Management depends essentially on whether the cause of obstruction (nearby inflammation, or adhesions) is amenable to treatment without resection or is manageable by resection only. Patient status, the degree of distension of the bowel proximal to the obstacle, and upstream faecal loading are other factors to consider. When the patient is extremely ill, or in the elderly or immuno-compromised patient, or when the grossly dilated colon is deemed unsuitable for anastomosis, a loop transverse colostomy,[46] Hartmann's procedure, or endoscopically-placed endoluminal stents are the possible options. However, the latter is fraught with potential re-obstruction and perforation.[47] Excessive faecal load may be reduced by on-table colonic lavage (via appendicostomy or terminal enterotomy).

CONCLUSION

In conclusion, complicated DD has many different aspects: each lead to varied but specific indications. Minimal invasive therapy, combined with less aggressive indications for radical surgery, should lead to fewer resections and/or stomas, reduced attendant morbidity and mortality, improved patient QoL, and cost-containment. Minimal invasive treatment of perforated diverticulitis with peritonitis might also be an option, but we will have to wait for the results of the three on-going trials.

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Botox: giving you more than just a pretty face!

BOTOX has been cleared as a safe, effective anti-cancer treatment, an international team of researchers has discovered.

In a study by international researchers, the role of the nervous system in cancer was explored, and it was found that, through the release of a neurotransmitter, the vagal nerve contributes to the growth of gastric tumours. Thus, in order to restrict tumour growth, scientists began testing methods in order to prevent this nerve from signalling to the tumour.

Prof Duan Chen, Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway, commented: "We found that by removing the effect of the nerve, the stem cells in the cancer tumour are suppressed, leading to cancer treatment and prevention."

Four different methods to sever connections between the nerve and the tumour were trialled: cutting the vagus nerve (vagotomy), administering local injections of botox to block the release of the neurotransmitter from the vagus nerve, administering drugs to block the receptor of the neurotransmitter, and knocking out the receptor gene.

All procedures successfully suppressed tumour growth, yet surprisingly, anti-cancer effects were most profound with local vagotomy and botox methods.

"We believe this treatment is a good treatment because it can be used locally and it targets the cancer stem cells," said Prof Chen.

One benefit of botox is that treatment only requires the patient to stay in hospital for a few hours; it is less expensive and less toxic than most standard cancer treatments, with very few side-effects.

"We found that by removing the effect of the nerve, the stem cells in the cancer tumour are suppressed, leading to cancer treatment and prevention."

Prof Duan Chen,
Norwegian University of Science and Technology,
Trondheim, Norway

Though researchers suggest that the best treatment is cutting the vagus nerve combined with traditional chemotherapy, botox could be considered as additional treatment for those who no longer respond to chemotherapy and benefit patients whose stomach cancer is deemed inoperable.

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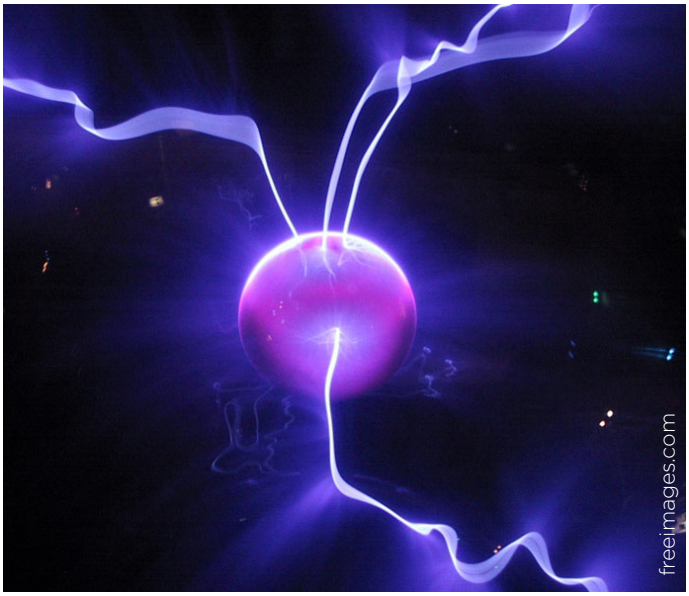
Electric pulse beats knife as liver damage probe



EVOLUTION of scanning technology has led to the revolutionary development of FibroScan, which has the potential to eliminate the need for painful invasive needle biopsies in liver disease patients. This FDA-approved device could significantly improve patient care and liver disease management.

Dr Shekhar Challa, Physician and President, Kansas Medical Clinic, Topeka, Kansas, USA, and his colleagues, are referring to the scan as a 'game changer' since it has great potential to dramatically reduce the need of liver biopsies by a staggering 90%.

According to the investigators, the device can be used to diagnose a wide range of liver diseases such as: non-alcoholic steatohepatitis, hepatitis B and C, fatty liver, and alcoholic liver disease.

"This device will save lives by letting us see the extent of damage that has already been done, and helping us to diagnose the proper treatment for what we hope will lead to an eventual recovery," said Dr Challa.

FibroScan utilises an ultrasound-based technology called Vibration-Controlled Transient Elastography which measures the fibrosis, or stiffness, of the liver. This, in itself, is a crucial element in the diagnosis of the organ's condition and the extent of damage sustained. Additionally, liver disease progression and subsequent treatment success can also be monitored by the device, providing healthcare professionals more information for the best course of treatment.

During the assessment, the patient is laid on his or her back, water-based gel is applied onto the skin, and a probe is then placed against the patient's skin. Vibrations are shuttled through the probe and into the liver by the FibroScan, which measures how long it takes for the vibration to travel through the liver; vibrations travel through diseased livers faster than healthy ones.

Dr Challa said that study data backed by FibroScan are accurate, or more accurate than liver biopsies, in determining fibrosis and cirrhosis.

"This device will save lives by letting us see the extent of damage that has already been done, and helping us to diagnose the proper treatment for what we hope will lead to an eventual recovery."

Dr Shekhar Challa, Gastroenterologist and President of Kansas Medical Clinic, Topeka, USA

Insulin guards against pancreatitis

"If we can better understand how insulin works, then we might be able to design new and more effective drugs that might one day provide the first curative treatment for this disease."

Dr Jason Bruce,
Faculty of Life Sciences,
University of Manchester,
Manchester, UK

PROTECTING pancreas cells from acute pancreatitis can be aided by insulin, scientists at the University of Manchester have proposed.

Every year in the UK, 20,000 patients are diagnosed with acute pancreatitis, an illness whereby the pancreas digests itself, resulting in severe abdominal pain, vomiting, and systemic inflammation. With no immediate treatment available, potential remedies are restricted to intravenous fluid and nutritional support.

According to Dr Jason Bruce, Faculty of Life Sciences, University of Manchester, Manchester, UK, major causes of pancreatitis include bile acid reflux from gall stones, excessive alcohol intake, and a diet high in fat. When alcohol and fat accumulate inside pancreatic acinar cells, the resulting molecules, called metabolites, deplete cellular energy levels and increase cellular calcium. This causes uncontrolled cell death - the cells burst, releasing toxic enzymes which digest the pancreas and surrounding tissue.

Yet, recent research has shown that insulin, released by the beta cells of the pancreas, can prevent the toxic effects of alcohol and fatty acid metabolites.

Insulin has previously been used to successfully treat obese pancreatitis patients by reducing fatty acids in the blood (diabetes makes pancreatitis worse and so diabetics are more at risk of developing the condition). Furthermore, incidences of pancreatitis are reduced in diabetics who receive insulin.

The study suggested that insulin may have a protective role in preventing pancreatitis; however, just how the insulin works in doing this remains unclear.

Dr Bruce explained: "Although more research is needed to confirm that insulin works in animal models and human clinical trials, this study suggests that, combined with tight control over blood glucose, insulin may be an effective treatment for pancreatitis.

"Furthermore, if we can better understand how insulin works, then we might be able to design new and more effective drugs that might one day provide the first curative treatment for this disease."

Spotted through blood test: Crohn's disease

BLOOD in children suffering from Crohn's disease, and the DNA changes found within it, could indicate ways to determine who will develop inflammatory bowel disorder (IBD); epigenetic changes could mean a better understanding of the condition and new treatments.

Despite alterations in gut microbes having been found in sufferers, what triggers the bowel disorder remains a mystery. Some suggest that an early exposure to antibiotics is responsible, whilst others point to *Mycobacterium avium* subspecies *paratuberculosis* (MAP) bacteria; mouse studies have shown that MAP causes inflammation, and its role in Crohn's disease remains under investigation.

Now a simple blood test could determine who would develop IBD. Prof Jack Satsangi, Chair of Gastroenterology, Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK, said that this study provides the strongest evidence that epigenetic changes are involved in Crohn's disease: "The findings provide a potential mechanism whereby diet or other environmental factors may modify genetic material to cause Crohn's disease."

Not everyone with indicative genes will develop the condition, although genes clearly play a role in the advancement of Crohn's, and researchers say that DNA testing would help identify who is at risk, potentially reducing numbers of patients needing further testing.

Additionally, chemical changes in genes detected by blood testing could lead to new treatments and help with monitoring patient responses to these. Investigators recently identified two gene areas in particular which are altered in children with the condition, and findings from the USA have identified a protein that can 'fix' Crohn's disease gene mutations.

Overall, there is no known way to prevent Crohn's disease; treatments involve trying to manage symptoms of IBD, which can lead to side-effects and multiple surgeries. However, understanding how genes work could help lead to future treatments for a disease that is both mysterious and debilitating.

"The findings provide a potential mechanism whereby diet or other environmental factors may modify genetic material to cause Crohn's disease."

Prof Jack Satsangi, Chair of Gastroenterology, Centre for Genomic and Experimental Medicine, University of Edinburgh, Edinburgh, UK

Rodent revolution aids war on liver disease

HOPES in the fight against liver disease have been raised by the discovery of a crucial inflammatory protein in a mouse model that, when hindered, stunts non-alcoholic fatty liver disease (NAFLD) evolution, and its advancement to liver cancer.

Strongly linked to the rising obesity outbreak, NAFLD afflicts 30% of Americans and, upon its development into non-alcoholic steatohepatitis (NASH) in many patients, it potentially triggers cirrhosis and hepatocellular carcinoma (HCC), the prime form of liver cancer.

However, a novel mouse model that closely matches human NASH has shown that blocking synthesis of tumour necrosis factor (TNF) and the binding to its receptor, using genetic tools or an anti-psoriasis and rheumatoid arthritis drug called Enbrel, prevents NASH and HCC incidence.

"These findings strongly call for clinical testing of relevant drugs in human NASH and its complications," said Dr Michael Karin, senior author, Distinguished Professor of Pharmacology, Laboratory of Gene Regulation and Signal Transduction, School of Medicine, University of California San Diego, La Jolla, California, USA. "Our research has shown that, at least in this mouse model, chemical compounds that include already clinically approved drugs that inhibit protein aggregation can also be used to prevent NASH caused by a high fat diet."

Mice were created through manipulation of a pre-existing mouse strain, MUP-uPA, which mimics the liver-damaging effects of a high-fat diet on humans. NASH and full-blown HCC were evident within 24 weeks and after 40 weeks, respectively, with tumours from the latter displaying an almost exact resemblance to human tumours. However, TNF interference curbed disease occurrence.

"Our research has shown that, at least in this mouse model, chemical compounds that include already clinically approved drugs that inhibit protein aggregation can also be used to prevent NASH caused by a high fat diet."

Dr Michael Karin,
Distinguished Professor of Pharmacology,
Laboratory of Gene Regulation and Signal Transduction, School of Medicine,
University of California San Diego,
La Jolla, USA

Dr Karin suggested that the studies will cause large ripples across areas grossly affected by a burgeoning obesity epidemic, and said: "In addition to developing a more suitable model for the study of NASH, this new work suggests some immediate targets for prevention and therapeutic intervention."

Sharing is caring after all, for the transportation of donor livers

> "Broader sharing of livers will not have much effect on CIT or negatively impact the liver transplant recipient, but will significantly increase the number of organs transported by flying."
>
> *Dr Sommer Gentry, Associate Professor, Mathematics Department, United States Naval Academy, Annapolis, USA*

COLD ischaemia time (CIT) will not significantly increase by a broader sharing of deceased donor livers.

A shortage of livers available for transplantation continues to be an issue in the USA, yet recent changes to allocation policy seek to address organ shortages and reduce geographic disparity (livers are offered at a regional level, to those at the highest risk of death, before being offered to local waiting list candidates). However, one concern with broader sharing is that transportation times may affect CIT, which could impair organ quality.

Researchers surveyed all organ procurement organisations to verify use of helicopters for transporting liver allografts, whether a central facility was used to recover the organ, and at which distance the mode of transportation changed from driving to flying. They further identified 111 centres that performed at least one adult liver transplant, along with hospitals that recovered at least one of the 1,284 deceased donor livers recovered in 2010, using the Scientific Registry of Transplant Recipients.

A detailed model of driving, helicopter, or airplane transport times between all hospitals was constructed, and results showed that median transport time, estimated for regionally shared livers, was 2 hours, compared to 1 hour for livers within local areas.

Median CIT was 7 hours for regionally shared livers versus 6 hours for those used in the local area; transport time comprised about 21% of CIT and variation in transport time accounted for approximately 15% of CIT variation.

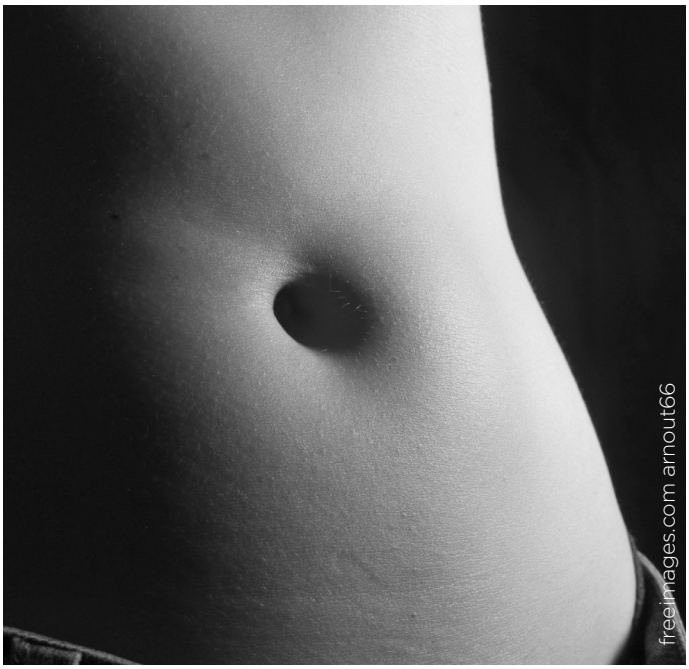
"Our findings indicate that non-transport factors impact CIT much more than transport time," concluded Dr Sommer Gentry, Associate Professor, Mathematics Department, United States Naval Academy, Annapolis, Maryland, USA. "Broader sharing of livers will not have much effect on CIT or negatively impact the liver transplant recipient, but will significantly increase the number of organs transported by flying."

Infiltrative drug is good news for Crohn's disease sufferers

VEDOLIZUMAB has become the first drug of its kind to tackle the symptoms of Crohn's disease (CD) from within the gut lining, providing another therapeutic option for 250,000 British sufferers.

Administered via infusion every 8 weeks, vedolizumab is the most promising step forward since drugs known as anti-tumour necrosis factors (TNFs) emerged in the 1990s. Posing as an attractive alternative for CD sufferers who do not respond effectively to current treatments, the drug targets inflammation that catalyses chronic symptoms including diarrhoea, bleeding, and fatigue.

2,700 subjects took part in trials testing the effectiveness of vedolizumab in centres such as London, Cambridge, and Cardiff. Upon testing, 40% of trial subjects taking vedolizumab were symptom-free for at least 1 year, with healing of the gut lining occurring in some subjects. Furthermore, twice as many CD subjects were symptom-free, compared to those treated with a placebo.



> "Now, for these patients who can face a lifetime of chronic symptoms, vedolizumab offers an additional treatment option with a completely new mode of action that specifically targets inflammation in the gut lining."
>
> *Dr James Lindsay, Consultant Gastroenterologist and UK Principal Clinical Trial Investigator, Barts and the London NHS Trust, London, UK*

Dr James Lindsay, UK Principal Clinical Trial Investigator and Consultant Gastroenterologist, Barts and the London NHS Trust, London, UK, said: "Over a decade ago, the introduction of anti-TNFs improved the management of ulcerative colitis and CD in patients with moderate-to-severe disease.

"Now, for these patients who can face a lifetime of chronic symptoms, vedolizumab offers an additional treatment option with a completely new mode of action that specifically targets inflammation in the gut lining."

A lifetime of treatment for CD, which often appears early in life, irrespective of diagnosis incidence, currently costs the NHS up to £720 million a year, putting the condition financially on the same level as diabetes and cancer. However, a course of vedolizumab costs around £12,000 per year, presenting obvious financial problems for many patients. The only alternative for CD patients who do not respond to the effects of current treatments is major surgery.

UK hit hardest for oesophageal cancer in men

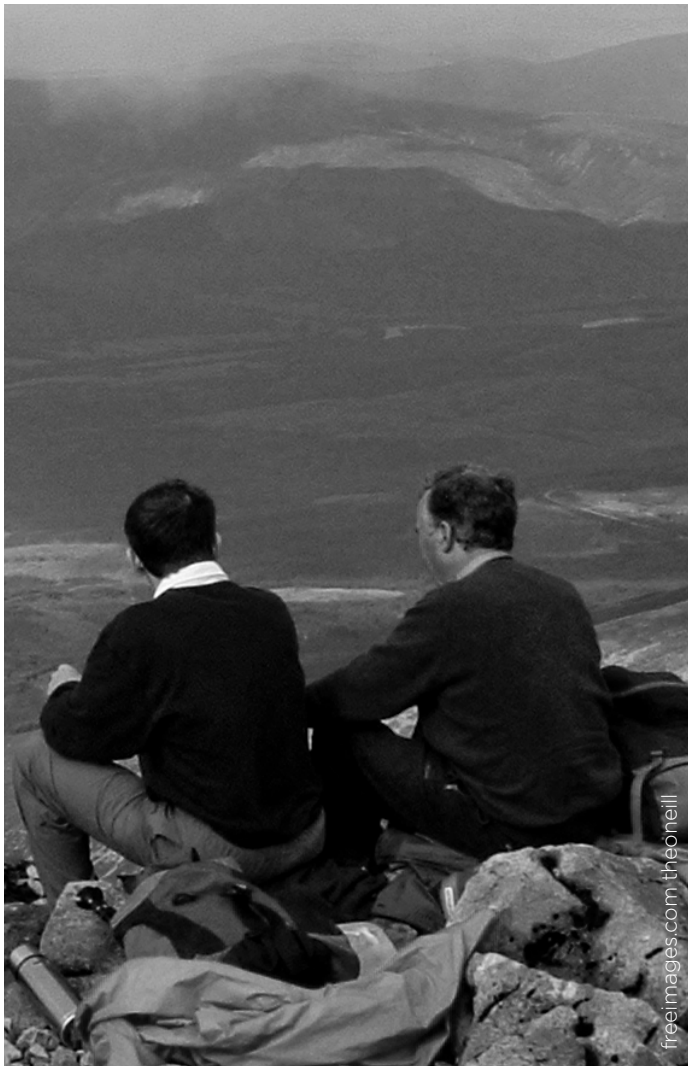
MEN are 4-times more likely to contract oesophageal cancer (OC), known as adenocarcinoma, than women; also the UK comes top for OC in men according to a comprehensive review of new worldwide cases from 2012.

The first ever efforts to quantify the global coverage of the two major types of OC - squamous cell carcinoma (SCC) and adenocarcinoma - were made through a study by the International Agency for Research on Cancer (IARC), the specialist cancer branch of the World Health Organization. Although SCC rates have fallen over the last several years, adenocarcinoma rates have increased, especially in high income nations, becoming the eighth most common cancer globally. Declining rates of *Helicobacter pylori* infection, which reduces stomach acidity (the strongest risk factor for adenocarcinoma), may explain this.

Men are more likely to develop both types of OC than women; this inter-gender pattern proved consistent worldwide, with a 3-fold increased likelihood of SCC incidence in men over women and a near 8-fold increase in Eastern Europe. 398,000 new cases of SCC and 52,000 of adenocarcinoma were recorded worldwide in 2012; this matches a new case rate of 5.2 and 0.7 per 100,000 of the population, respectively. 80% of the total caseload, 315,000 cases, occurred in East and South East Asia alone, while sub-Saharan Africa and Central and South America hosted 13,000 and 12,000 cases, respectively.

The greatest number of new adenocarcinoma cases (12,000) occurred in Northern and Western Europe, and South East Asia and

Although SCC rates have fallen over the last several years, adenocarcinoma rates have increased, especially in high income nations, becoming the 8th most common cancer globally.



North America hosted 11,500 and 11,100 new cases, respectively. Although the US had the highest number of new cases in 2012 (10,000), according to the age structure of different populations it was actually the UK which had the highest number of new cases (7.2/100,000 in men, 2.5/100,000 in women), trailed by the Netherlands, the Republic of Ireland, Iceland, and New Zealand.

Drug discovery could spell BAD news for chronic diarrhoea

"This drug represents a new potential approach to treating BAD by restoring levels of the FGF19 hormone and so controlling bile acid production in the liver."

Prof Julian Walters, Imperial College London, London, UK

ENCOURAGING effects of a new drug on relieving the symptoms of chronic diarrhoea have emerged, raising hopes for a solution to a highly disruptive illness.

Bile acid diarrhoea (BAD) causes chronic diarrhoea in 1 in 100 adults in Western countries, but is often confused with irritable bowel syndrome (IBS) by doctors, causing unnecessary repeat testing due to inaccurate diagnosis. Prof Julian Walters, Department of Medicine, Imperial College London, London, UK, said: "Many doctors are totally unaware of BAD, but it is more common than Crohn's disease and ulcerative colitis. When patients are correctly diagnosed, there are specific treatments that can help them, but many people find these current drugs are unpalatable.

"The condition often has a serious impact on patients' work and social lives, causing people to have up to ten watery bowel movements a day, often for many months, with an urgent need to go to avoid accidental incontinence."

BAD patient relief could lie in obeticholic acid (OCA) - the first in a new class of drugs called farnesoid X receptor (FXR) agonists - since patient response to OCA exposes abnormalities in the targeted system that could be crucial in BAD onset. A hormone secreted in the ileum, FGF19, controls bile acid production in the liver, while past research highlights low levels of FGF19 in BAD patients; OCA targets ileum receptors which kick-start FGF19 production. OCA administration catalysed improved symptoms in primary BAD subjects and some secondary BAD subjects in a pilot study, and treatment was well tolerated overall.

"This drug represents a new potential approach to treating BAD by restoring levels of the FGF19 hormone and so controlling bile acid production in the liver. These early findings suggest that FXR agonists could be effective for treating patients with chronic diarrhoea. This is exciting and we need larger studies to confirm this," concluded Prof Walters.

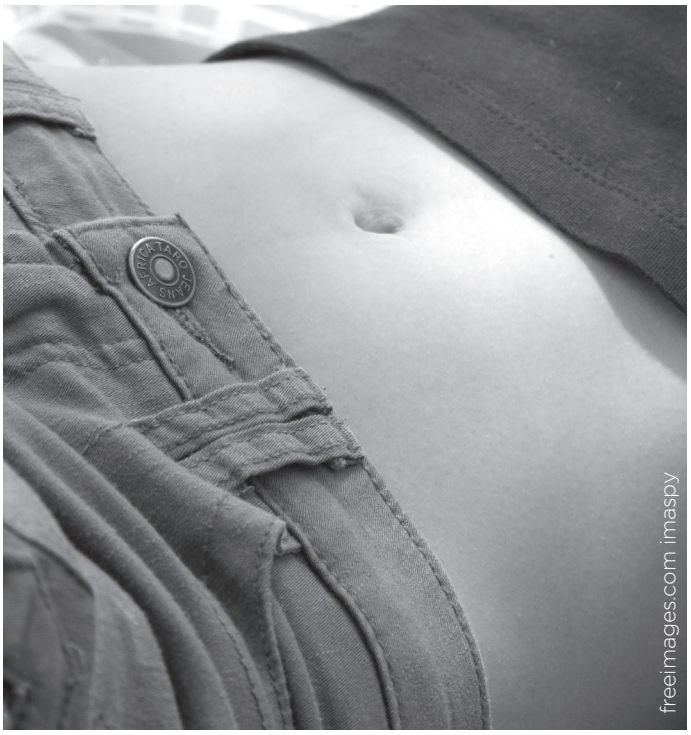
Growing an intestine for GI diseases

"This provides a new way to study the many diseases and conditions that can cause intestinal failure, from genetic disorders appearing at birth to conditions that strike later in life, such as cancer and Crohn's disease."

Dr Michael Helmrath,
Surgical Director of the Intestinal Rehabilitation Program,
Cincinnati Children's Hospital Medical Center,
Cincinnati, USA

PERSONALISED human intestinal tissue may be within reach for the treatment of gastrointestinal diseases following the successful transplantation of 'organoids' of fully functioning human intestines (made with induced pluripotent stem cells [iPSCs]) into mice, potentially preventing transplant rejection and ending the need for lifelong medication.

Able to change into any body tissue type, iPSCs are extracted from adult cells, as shown in a study by Dr Michael Helmrath, Surgical Director of the Intestinal Rehabilitation Program, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA, and colleagues, which involved growing 'blank' iPSCs using human adult cells from skin and blood samples. The addition of iPSCs to a 'molecular cocktail' catalysed transformation into intestinal organoids, miniature structures resembling intestines.



Organoid transplantation into the kidneys of mice succeeded due to incorporation of genetically modified immune systems. This allowed them to accept the organoids, which thrived into mature human intestinal tissue and multiplied in the presence of an optimal blood supply. According to Dr Helmrath, the mucosal lining, which houses all the differentiated cells, constantly replenishes itself through intestinal stem cell proliferation. It also develops the ability to absorb and digest, while the layers of intestinal muscle grow; this is crucial.

"This study supports the concept that patient-specific cells can be used to grow [an] intestine. This provides a new way to study the many diseases and conditions that can cause intestinal failure, from genetic disorders appearing at birth to conditions that strike later in life, such as cancer and Crohn's disease. These studies also advance the longer-term goal of growing tissues that can replace damaged human intestine," said Dr Helmrath.

Many years of research are required before this method can be applied to medical practice. However, researchers stress that being able to test drugs in models of human organs could slash years of developing new drugs.

Buzz off cancer!

"Our results in fruit flies led us to think that Irx transcription factors such as Mirror might play a similar role in flies and humans, namely reducing the ability of tumour cells to respond to TGF-β in the transition from a benign adenoma to more aggressive carcinoma in the human colon."

Dr Andreu Casali,
Institute for Research in Biomedicine,
Barcelona, Spain

DROSOPHILA may help shed light on the progression of colorectal cancer (CRC) in humans; findings show similar genes and genetic interactions in cultured CRC cells and a transcription factor in fruit flies.

A transcription factor in *Drosophila* flies, known as 'Mirror', has recently been seen to regulate tumour-like growths in the intestines of the insects, enabling Spanish scientists to hypothesise that a similar system may influence the progression of human CRC.

"We have been able to use flies as a model system to study molecular events that are very similar to the steps that take place in CRC in humans, and we have been able to use this system to identify new genetic regulations relevant to human disease," commented Dr Andreu Casali, lead study author and Research Associate, Institute for Research in Biomedicine, Barcelona, Spain.

Researchers found mutations in two signalling pathways known to activate tumour-like growths in the flies' intestines: the Wnt and epithelial growth factor receptor/Ras pathways. Activity in the decapentaplegic (Dpp) pathway supresses the growth of these intestinal tumours; however, this is counteracted by a specific type of Irx transcription factor – Mirror.

In humans, the equivalent of Dpp is bone morphogenetic protein, one component of the transforming growth factor-beta (TGF-β) signalling pathway. Dr Casali explained: "Our results in fruit flies led us to think that Irx transcription factors such as Mirror might play a similar role in flies and humans, namely reducing the ability of tumour cells to respond to TGF-β in the transition from a benign adenoma to more aggressive carcinoma in the human colon."

Thus, transcription factors could, under certain conditions, favour cell growth, leading to cell proliferation consistent with signs of cancer in flies and humans. It may now be possible to test potential interventions for these processes, using *Drosophila* as a model system.

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Gastroenterology

Endochoice is a medtech firm that aims to manufacture and commercialise a plethora of platform technologies such as devices, infection control, and endoscopic imaging designed for specialists in the treatment of a large variety of gastrointestinal (GI) diseases. The company has quickly compiled a proprietary product portfolio since its inception in 2008, including the revolutionary Full Spectrum Endoscopy® System (Fuse®); this System enables doctors to better observe the GI tract for diagnosis and treatment. Endochoice collaborates with 34 global distribution partners, leveraging its direct sales organisation to cater for over 2,000 USA-based customers.

Ferring Pharmaceuticals Ltd. has a product portfolio that demonstrates an innovative and successful track record in urology, endocrine oncology, gastroenterology, endocrinology, and reproductive health. The company has developed strong expertise through the development of technologies that facilitate the use of peptide and protein compounds, and is thus able to capitalise on its position as one of the world's leading companies in this field of chemistry. Ferring has a powerful global presence, and its products are distributed across more than 70 countries. In-house manufacturing is carried out in Switzerland, Denmark, Germany, Czech Republic, and China.

Boasting an independent science research base fuelling the development of a range of generic drugs, PRO.MED.CS Praha a.s. is a leading Czech pharmaceutical company that has assumed a commanding position on Western European markets in recent years. Exporting its products to over 25 countries, including Central and Eastern Europe as well as Central Asia, PRO.MED.CS strives to distribute proven, effective, and safe products at a reasonable price. The company focuses on treating gastrointestinal, cardiovascular, and musculoskeletal conditions through the production of tablets and coated tablets and capsules, with over 1.5 million of these produced daily.

Takeda is currently the largest pharmaceutical company in Japan, and is one of the main global healthcare players. The company has based its philosophy on the concept of 'Takeda-ism' (integrity, fairness, honesty, and perseverance), which has been developed over the company's 230-year lifetime. Following this, Takeda carries out its activities through the company slogan: "Strive towards better health for people worldwide through leading innovation in medicine." The Osaka-based firm has over 30,000 employees in more than 70 countries and regions worldwide. Takeda's pharmaceutical products have been marketed in around 100 countries.

VSL Pharmaceuticals, Inc. specialises in supplying a range of medical foods aimed at helping patients to manage their diets. The company's flagship product is VSL#3, a probiotic medical food which helps patients who are suffering from ulcerative colitis, irritable bowel syndrome, and ileal pouch. VSL#3 contains a number of beneficial live bacteria, which protect the gastrointestinal tracts and aid the dietary management of ulcerative colitis. VSL#3 is the world's most concentrated probiotic, with 450 billion beneficial bacteria in every sachet. The probiotic exceeds competitor products, with other probiotic dietary supplements possessing a much lower bacterial count.

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UPCOMING EVENTS

European School of Oncology-European Association for Gastroenterology, Endoscopy and Nutrition (ESO-EAGEN) Masterclass in Endoscopy in Gastrointestinal (GI) Oncology

30th January-2nd February 2015

Magdeburg, Germany

The aim of this multidisciplinary course is to provide an update on the role of endoscopy in the diagnosis and treatment of GI neoplasias. It is specifically addressed to young specialists, and each topic will cover all levels of procedures, from basic to the most complex and difficult. The course will consist of a series of presentations, updated lectures, and video sessions. Live endoscopy sessions will also be performed by a faculty of experts.

10th Congress of European Crohn's and Colitis Organisation (ECCO) Inflammatory Bowel Diseases (IBD)

19th-21st February 2015

Barcelona, Spain

The comprehensive and exciting scientific programme will be structured around basic science, translational medicine, and clinical sessions, delivered by the world's top specialists. The focus of the event will be on all aspects of IBD including: adult and paediatric care, medical and surgical advances, costs and quality of care, and environmental involvement. It also includes oral presentations and summaries of new ECCO guidelines.

International Conference on Gastroenterology, Hepatology and Nutrition (ICGHN) 2015

23rd-24th February 2015

London, United Kingdom

Leading academic scientists, researchers, and research scholars will convene to exchange and share their experiences and research results on all aspects of gastroenterology, hepatology, and nutrition. This conference will provide the premier interdisciplinary forum for researchers, practitioners, and educators to present and discuss the most recent innovations, trends, concerns, practical challenges, and the solutions to be adopted in this medical field.

The 5th Biennial Congress of the Asian-Pacific Hepato-Pancreato-Biliary Association

18th-21st March 2015

Singapore

This Congress will aim to provide a platform for the exchange of scientific knowledge on the latest developments on hepato-pancreato-biliary disorders. There will be an exciting line-up of expert speakers including top practitioners, opinion leaders, and researchers. This event will comprise of an interesting range of plenary sessions, presentations, and video screenings. There will be a host of networking opportunities for delegates to meet with experts.

European Society of Gastrointestinal and Abdominal Radiology (ESGAR) 2015 - 26th Annual Meeting and Postgraduate Course

9th-12th June 2015

Paris, France

This meeting offers a high quality scientific programme, which is the cornerstone of its success. The programme will appeal to both specialists in GI radiology and novices with a budding interest in the field. There will be active involvement in clinical cases, lecture sessions, symposia, poster presentations, and workshops. Video case presentations will also be utilised to emphasise the latest practical aspects and procedural tips/tricks.

The British Society of Gastroenterology (BSG) Annual Meeting 2015

22nd-25th June 2015

London, United Kingdom

This multidisciplinary meeting will cover all aspects of medical and surgical gastroenterology and hepatology with cutting edge clinical and basic science research. The scientific programme will include poster presentations, workshops, lectures, and clinical symposia on a wide range of topics. Additionally, there will be an integrated nurse training programme which will span 3 days of the meeting. This meeting will be of benefit to gastroenterologists, hepatologists, nurses, radiologists, dieticians, and others interested in the field.

American College of Gastroenterology (ACG) Annual Meeting & Postgraduate Course CME

16th-21st October 2015

Honolulu, USA

Participants will have unparalleled access to the latest clinical information on key topics, which will be delivered in a series of stimulating lectures, workshops, plenary sessions, and presentations. The trainees' forum will allow young physicians to explore career opportunities along with the opportunity to meet the faculty for in-depth discussions. There will also be industry exhibitions featuring the latest advances in GI technology and therapeutics.

United European Gastroenterology (UEG) Week

24th-28th October 2015

Barcelona, Spain

Cementing its reputation as the largest and most prestigious meeting in Europe, this event will bring together healthcare professionals from around the world to improve the standards of care in gastroenterology, and promote the understanding of digestive and liver diseases. The scientific programme comprises of a wide range of presentations, live endoscopy sessions, and interactive clinical case symposia including: 'Today's science; tomorrow's medicine'.

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