TREATMENT STRATEGIES
GASTROENTEROLOGY

Volume 2 Issue 1

Including
- Crohn's Disease
- Endoscopy
- Esophageal Disease
- H. Pylori
- Hepatitis
- IBS
- Liver Disease
- Lower Gastrointestinal Disorders
- Pancreatic Cancer
- Stenting

Papers include:

Includes a review of the 21st UEG Week 2013

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TREATMENT STRATEGIES - GASTROENTEROLOGY

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Welcome...

I am delighted to welcome you to the second edition of *Treatment Strategies - Gastroenterology*. In our 2013 edition we bring you a wealth of informative articles as well as an in-depth review of United European Gastroenterology (UEG) Week 2013, which took place in Berlin this October. UEG is a non-profit organisation which is made up of all of the leading European Societies concerned with digestive diseases. Over 12,500 delegates from 125 countries were in attendance at the event and over 3,500 abstracts were submitted. Our review will bring you all of the breaking news, awards, research highlights and products, as well as a number of poster synopses.

This edition also features a number of informative papers on subjects such as Crohn's disease, endoscopy, hepatitis and IBS among others These carefully selected papers will offer new insights into the latest treatment strategies for a number of gastroenterological issues. We really feel that these papers bring something new to the field, and so we hope you enjoy these articles.

Here at The Cambridge Research Centre we are always looking for new ways to bring you our content, and this year we have launched our growing range of interactive eBooks on iBooks, which is a great new way to read and download our content on your devices. We also launched our Treatment Strategies TV channel, where you can find footage from all of the most important scientific conferences, as well as interviews, symposia proceedings, and much more. The team are also all active on Twitter and LinkedIn, and please do follow us or join our LinkedIn group to find out more about our upcoming releases.

We hope that you enjoy this edition of *Treatment Strategies - Gastroenterology*, and please do let us know your thoughts about this latest issue. We look forward to our gastroenterology title becoming one of our most successful publications, and look out for our 2014 publication, which will feature a review of UEG Week 2014.

Hannah Corby, Chief Sub-editor

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

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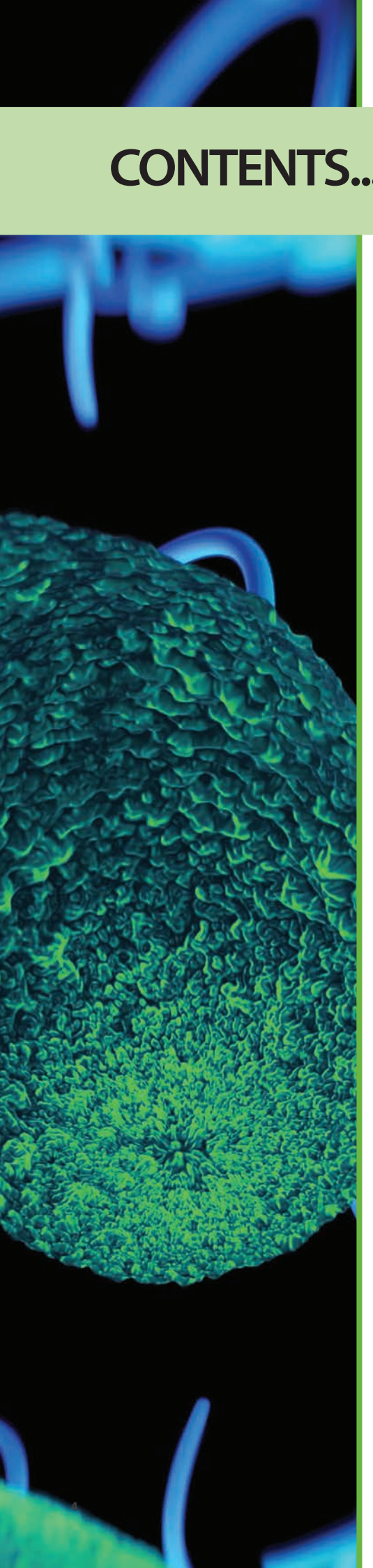

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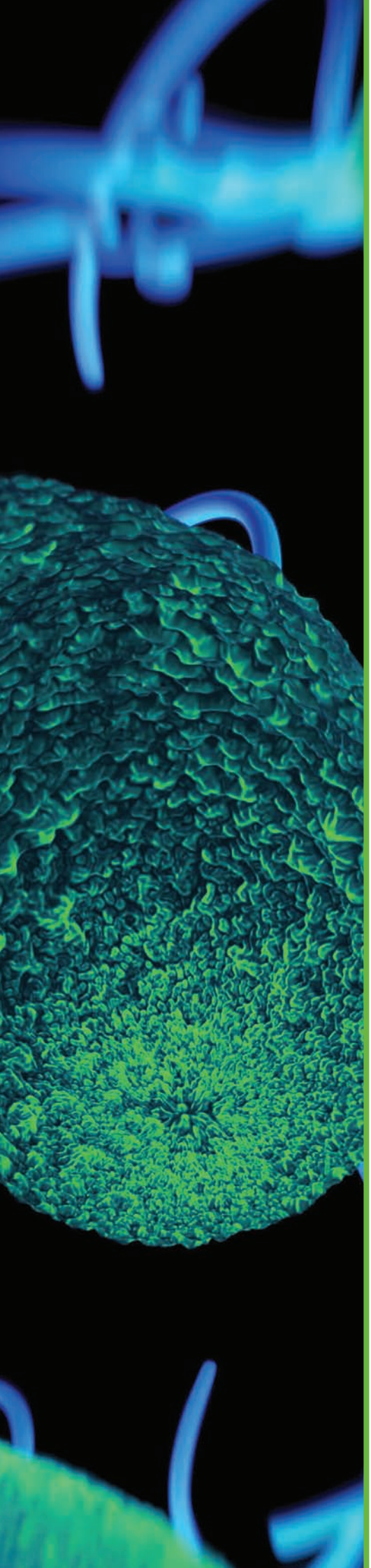

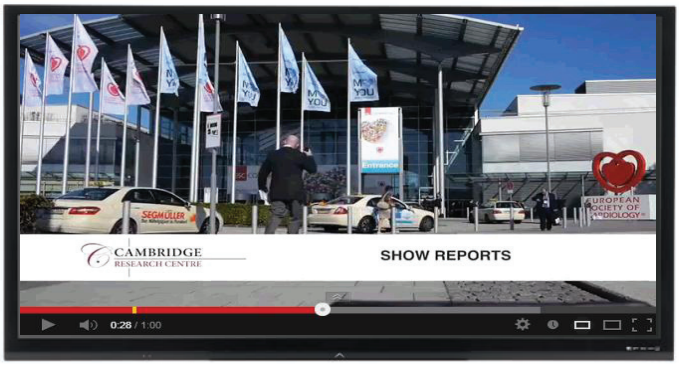

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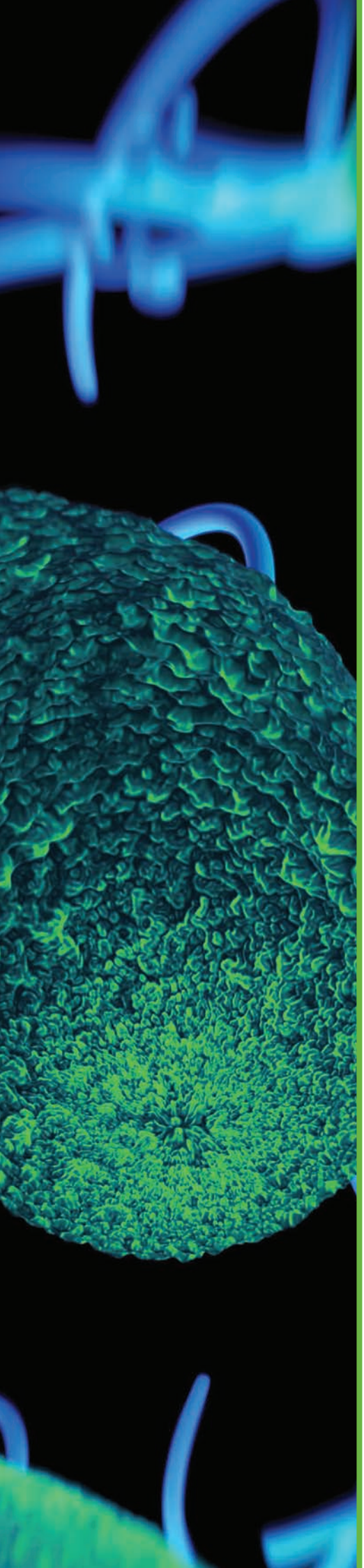

EDITORIAL ADVISORY PANEL

Foreword

C.M. Frank Kneepkens
Department of Paediatrics, VU University Medical Centre, Amsterdam

Welcome to the second edition of *Treatment Strategies – Gastroenterology*. This edition aims to build on the success of the inaugural publication, and offers a wealth of papers which detail the latest updates and developments in the field of gastroenterology.

Children are not little adults and paediatric gastroenterology is not a smaller version of adult gastroenterology. The differences between the two disciplines are as big as the similarities. While much of the effort in adult gastroenterology goes into colon cancer and related conditions, in PedGI – as it is fondly abbreviated – the emphasis is on conditions with congenital and developmental issues. Above that: growth is always involved. In children, every condition and every treatment may have an impact on growth and development. On the other hand, children may outgrow their problems.

Yet, PedGI would be nowhere without its big brother. Almost every (benign) 'adult' gastroenterological condition is also seen in children. In some, PedGI clearly has the lead – as with coeliac disease –, but mostly we have to lean on and learn from the adults. With IBD as an example, several reasons can be given for this dependency. Firstly, in children IBD, although increasing in incidence, is relatively rare. It is therefore difficult to gather enough experience to be able to tackle all possible complications – and childhood IBD is usually more severe than in adults. Secondly, most paediatric gastroenterologists could not dream of acquiring the same dexterity as their 'adult' colleagues. Every now and then we need to call for their help. Finally, and most importantly, therapeutic studies in children are subject to several restrictions. It is only after indications and dosages for adults are established that paediatric drug studies can be initiated. Obviously, it is important that these studies be done, as side-effects and complications may differ between children, with their changing body size and composition, and adults.

With this in mind, what challenges is PedGI facing for the near future? One major issue, again, is the care for children with IBD. Paediatric IBD is not only often more serious and more difficult to treat, it will also last considerably longer, with an increasing risk of complications. For instance, infliximab loses its effect in time in up to 50% of children. Furthermore, quality of life is diminished, psychological development is under pressure and future unemployment is a great risk; aspects that especially need to be addressed during transition to adult gastroenterology. This asks for both redesigning long-term treatment strategies and the development of comprehensive care programmes, for which multicentre initiatives such as the ImproveCareNow collaborative network and the ESPGHAN IBD Porto Group are essential instruments.

And there is more. Since 'Rome II' criteria for functional bowel disorders are also available for children. With the Rome IV criteria underway, it has to be recognised that both clinical applicability and discriminatory power with regard to somatic disease of these mainly consensus-based criteria are limited, that etiology and pathophysiology are largely unknown and that there is almost no effective treatment. Given the high prevalence of these conditions in children and their effect on quality of life and development, the study of these issues should be given priority.

But PedGI also provides new challenges for adult gastroenterology. Thanks to improved surgical skills and new possibilities, children with serious congenital conditions such as congenital diaphragmatic hernia, abdominal wall defects, Hirschsprung's disease, rectal atresia, short bowel syndrome and biliary atresia – to name a few – now will survive to become adults. This also holds true for neurologically damaged children, requiring knowledge on feeding techniques as much as nutritional needs. Adult gastroenterologists have to learn to deal with these, previously exclusively paediatric, problems. Clearly, while the future of PedGI may be visible through the acquirements of present-day adult gastroenterology, the latter should keep an open eye to the former as well.

C. M. Frank Kneepkens has a long-standing career as a paediatric gastroenterologist. His main interests are functional gastrointestinal diseases, cow's milk allergy and allergy prevention, eosinophilic oesophagitis and coeliac disease. He has been involved in the development of several guidelines and is an editor of various national and international journals and of a well-received Dutch paediatric workbook series.

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UEGW Meeting 2013

12–16 October, Berlin

21st United European Gastroenterology Week

INSIDE...

The Meeting

The Exhibition

Sara Taheri, Treatment Strategies, is delighted to bring to you our review of the 21st UEG Week 2013. This review features all of the breaking news, awards, research, and highlights of the most important symposia proceedings, as well as the most innovative products from the meeting. This review is followed with a series of posters that were showcased at the event, the findings of which will have a direct impact upon the future of gastroenterologic medicine.

The United European Gastroenterology (UEG) is a professional non-profit organisation that combines all of the leading European societies concerned with digestive diseases. The UEG's mission is to continually improve the standards of care in gastroenterology, and promote a greater understanding of digestive and liver disease.

UEG has been holding an annual meeting since 1992, in which scientists from all over the world can present their latest research in digestive and liver diseases and, as ever, this year's attendees had the opportunity to obtain first-hand expert information on diseases of the stomach, bowel, oesophagus, liver, pancreas and gallbladder.

The 21st United European Gastroenterology Week (UEG Week) was held on 12-16 October 2013 in Internationales Congress Centrum Berlin (ICC Berlin).

Indeed, UEG Week has become the largest and most prestigious gastroenterology meeting in Europe. It has, over the years, developed on a global scale, attracting over 12,000 participants each year from more than 120 countries, with numbers steadily rising. Local and international speakers were available to answer a range of questions from attendees at two press conferences and at the press centre.

Special themes focused on translating science into clinical practice and the role of guidelines, standards and pathways for clinicians at UEG Week 2013. There were two full days of live endoscopy, a focus on IBD, a continuing look at the expanding role of gastroenterologists in GI oncology together with an abundant number of lectures by world-renowned experts and rising stars.

The meeting began with an opening plenary session, which included official speeches and the opening of the scientific programme with a mixture of invited speakers and presentations of the best submitted abstracts. The UEG Research Prize and the Lifetime Achievement Award were also presented at the Plenary Session.

As usual there was plenty of interactivity during the meeting with voting sessions, clinical cases, debates and tandem talks. Oral presentations of original research increased in prominence this year, with a more interactive format. These sessions allow the presentation of the best, original research submitted and lively discussion and debate. This was an excellent opportunity to hear about GI and liver research in Europe and worldwide before it is published, and to question the researchers.

Additionally, this year there was also the introduction of more innovations

including panel discussions and 'Chat with the Speakers' sessions. Symposia labeled 'Chat with the Speakers' were a new feature for UEG Week 2013. These were scheduled either before a lunch break or at the end of day and allowed attendees to sit with the speakers in small groups, ask questions, discuss relevant cases, gain advice and set up collaborations.

"Today's science; tomorrow's medicine" is part of a new initiative that provides a platform for gastroenterologists and hepatologists to learn how this important field will impact their disciplines in every day practice. The initiative consisted of a two day cutting edge symposium that featured experts from around the world who described the latest research on genetics and pathogenesis aspects of GI and liver diseases. Special attention was given to how these discoveries will reshape the future of clinical practice.

Another highlight of this year UEG week was the 'wrap up sessions' which provided delegates with a comprehensive summary of the major areas in GI and liver disease of recent changes in management, major research publications and important advances.

Video Case Session provided an excellent platform for information on very current issues of endoscopy. During this session short videos showing examples of new, unexpected, or exceptional endoscopic practice were presented and briefly discussed.

In response to the request from previous meetings, live endoscopy was included in the main programme and in the Postgraduate Teaching Programme. Top international experts demonstrated cutting-edge techniques and new tricks in a lively and exciting format. The use of multiple parallel cases and experienced chairman ensured interactive learning.

Posters were displayed from Monday until Wednesday, and there were Poster Rounds with Selected experts who lead the discussion with other members attending the poster session. The presenters gave a summary of the major findings and experts lead the discussion with other members attending the poster session.

Each day a poster prize for the 'Top Poster' in the major categories were awarded:

- Liver and pancreatic disease
- Upper gastrointestinal disease
- Lower gastrointestinal disease
- Surgery, endoscopy, imaging

www.ueg.eu/week

Berlin...

Berlin was an ideal venue to host the 21st United European Gastroenterology Week. The city is best known for its historical associations as the German capital, internationalism and tolerance as well as its lively nightlife, cafés, clubs, and bars. With numerous museums, palaces, and other sites of historic interest there is a lot on offer for visitors and attendees of the event.

Berlin is more than 775 years old and many monuments and landmarks have been built across the city by generations.

The city has had a turbulent history, and as a result the city has many distinctive neighbourhoods. It is possible to see many different historic periods within the city centre, from a few surviving medieval buildings near Alexanderplatz, to the ultra modern glass and steel structures at Potsdamer Platz.

There is also varied range of architecture and, although some buildings were badly damaged in the final years of World War II and broken apart during the Cold War, there has been a great reconstruction, especially with the reunification push after the fall of the Berlin Wall in 1989.

The Brandenburg Gate is situated at the end of Unter den Linden, a grand boulevard in Berlin. It was originally part of a wall surrounding Berlin and was the main entrance to the city. It is the only gate that remains of this former city wall.

The Brandenburger Tor is a monumental gate built in the 18th century as a symbol of peace. During the Cold War, when the gate was located right near the border between East and West Berlin, it became a symbol of a divided city. Indeed, the desolated Pariser Platz has now been completely redeveloped and has regained much of its nineteenth-century grandeur.

The Reichstag, the seat of the German Parliament, is one of Berlin's most historic landmarks. It is close to the Brandenburger Gate and before the unification, it was located right next to the Berlin Wall.

The Berlin Wall, which separated the city in an eastern and western part, was the symbol of the Cold War. After the second world war, defeated Germany was divided up into 4 parts: an American, British, French and Soviet occupation zone.

Most of the Berlin Wall has been demolished since the border between East and West Berlin opened in 1989, but some parts still stand. The most famous one is the 1316m long East Side Gallery. It is located along Mühlenstrasse between Warschauer Strasse and the Ostbahnhof and contains 106 paintings.

The official Berlin Wall Memorial Site can be found at Bernauer Strasse - the site of many escapes from East to West Berlin and also the place where the official destruction of the Wall started. Here you can overlook an intact section of the wall, complete with security zone and watchtower from an observation deck opposite the street.

Other, smaller sections can be found around Potsdamer Platz, the Reichstag, Invaliedenfriedhof, Bornholmer Strasse, Nieder-kirchner Strasse and Zimmerstrasse near Checkpoint Charlie.

The ESGE Learning Area

The European Society of Gastrointestinal Endoscopy welcomed all delegates of the UEG Week to the ESGE Learning Area. The mission of the ESGE is to promote good endoscopy, support training and teaching activities, and at the UEG Week they provided a platform for live encounter and interaction with renowned experts in the field.

The European Society of Gastrointestinal Endoscopy opened their ESGE Learning Area to all of the delegates that attended UEG Week 2013. ESGE's mission is to promote good endoscopy and to support training and teaching activities. At the UEG Week they aimed to provide a platform for live encounter and interaction with renowned experts in the field.

The ESGE Learning Area was divided into three sections:

• The Hands-On Training Centre, which offered, in co-operation with ESGENA, various forms of hands-on training throughout the congress.

• The Lecture Theatre, which offered lectures on selected topics and provide an opportunity for small forum discussions with experts.

• The DvD Learning Centre, which had several DvD stations offering individual learning for endoscopy.

The Hands-On Training Centre provided delegates with sessions in basic and advanced endoscopy with the experts. The 90-minute training sessions in the Hands-on Theatre offered a unique access to state of the art endoscopic equipment and accessories. Participants had the opportunity to look, learn, ask questions and perform techniques themselves under personal doctor and nurse tutoring.

In cooperation with ESGENA, the aim of this activity was to increase the awareness of diagnostic and therapeutic techniques and to enable delegates to checking their skills. This year the scope of procedures and sessions had to be extended to give even more insight into good and current endoscopy.

ESGE DVD Learning Centre offered all delegates the opportunity to view the latest teaching material on video screens with headphone sound transmission. Case studies from the ESGE DVD Encyclopaedia were complemented by select video submissions from American Society for Gastrointestinal Endoscopy (ASGE) and the Japan Gastroenterological Endoscopy Society (JGES).

In the ESGE Lecture Theatre highly qualified and well-known endoscopists presented their views and experience on current endoscopic procedures and techniques. Their counterparts in discussion are equally well-known, and in several cases were more senior specialists whose role was to moderate the talk and perhaps critically question the case at hand.

UEG Week Awards

The UEG Lifetime Achievement Award recognises out-standing individuals whose pioneering and inventiveness throughout their careers have improved the Federation and inspired others.

The recipient of this year's UEG week Lifetime Achievement Award was Prof. Giovanni Gasbarrini.

Prof. Gasbarrini is a pioneer in pathophysiology of gastric, intestinal and liver disorders on a national and international level. He performed pioneering work in the field of Helicobacter pylori in particular by studying extra digestive diseases, for example the idiopathic throm-bocytopenic purpura, which is now recognised as a consequence of the infection. He also developed new eradication therapies such as levofloxacin-based triple therapy. He has shown a life-long commitment to research and teaching, and has been a key person in the foundation and organisation of more than 150 international scientific societies and meetings.

The teaching activities of Prof. Gasbarrini are highlighted by the fact that many of his fellows and collaborators hold important positions in national and international academic institutions. Prof. Gasbarrini followed the footsteps of his father, who was a leading European gastroenterologist, and is being followed by his son Antonio who is the secretary of the Italian Society for Study of the Liver.

He was a founding member of one of UEG's ordinary member societies, the European Helicobacter study Group (EHsG). He was also President of the European Association for Gastroenterology, Endoscopy and Nutrition (EAGEN) and in this capacity he was instrumental in creating the medical block that is represented on UEG Council.

Research Prize

This prize is awarded for excellence in basic science, translational or clinical research and for demonstrating that the work has had an impact in its field and has been recognised internationally.

Prof. Ian Tomlinson, Group Head at the Wellcome Trust Centre for Human Genetics in Oxford was awarded with the UEG Research Prize together with 100,000 euros.

A world-renowned expert in GI cancer genetics, Prof. Tomlinson's work focuses principally on cancer predisposition and related fields. In less than 20 years he was able to identify more than 20 genes, which increase the risk of colorectal cancers, representing the majority of all known bowel tumour genes.

"We believe we have identified an important new pathway that affects bowel cancer predisposition and we want to move this work forwards to maximise patient benefits in the future."

The Prize is to support his research project titled "The roles of bone morphogenetic protein pathway genes in the normal and neoplastic intestines".

Prof. Tomlinson said he was honoured to have been awarded the prize. "We are delighted that we can now continue our work looking at genetic risk factors for colorectal cancer," he says.

Rising Stars Award

The UEG National Societies Committee and the Scientific Committee jointly select up to 10 emerging clinical scientists. Researchers are awarded Rising Star status based on a track record of international-quality research and developing scientific independence. This initiative provides a durable platform for young researchers so that they can give state-of-the-art lectures and chair scientific sessions at UEG Week.

This year's Rising Stars include; Francesc Balaguer, Spain; Tine Jess, Denmark; Johanna Laukkarinen, Finland; Georgia Malamut, France; Michael Quante, Germany; Harry Sokol, France; Augusto Villanueva, Spain; and Thomas von Hahn, Germany.

The meeting is designed to attract young investigators by offering scholarships and acknowledging excellence by awarding prizes for the best posters. The 12 top posters were awarded a prize on basis of scientific merit using the evaluation process of the UEG Scientific Committee.

The Award Ceremony was held each day for the 'Top Poster' in each of the four major categories; Liver and pancreatic disease; Upper gastrointestinal disease; Lower gastrointestinal disease; surgery, endoscopy, imaging. The prize winners received free entry to the Postgraduate Training Programme of the next year's UEG Week.

National Colorectal Cancer Screening Programme Proclaimed a Success

A national colorectal cancer (CRC) screening programme with colonoscopy has been proclaimed a success, after the largest study of its kind found high rates of cancer detection and low rates of complications. The study, which evaluated the outcomes of almost three million screening colonoscopies in Germany, found that experienced endoscopists were able to detect and remove a significant number of early- stage cancers and pre-cancerous growths, potentially saving thousands of lives.

"We think the results of this study are extremely encouraging and confirm the benefits of this approach," says Dr. Christian Pox from the Medical University Clinic in Bochum, Germany, who presented the results of this landmark study at the first of two press conferences during UEG Week 2013.

During this press conference Dr. Christian Pox described the urgent need to initiate a national CRC screening programme in Germany. Dr Pox continued to explain why colonoscopy was chosen as the preferred screening approach when the programme began in 2002.

The study has revealed high rates of detection of early-stage cancers and pre-cancerous growth – particularly in men – providing an unprecedented opportunity to prevent or cure CRC. However, as participation rates in the screening programme remain low Dr. Pox summarised what can be done to encourage more eligible people to come forward for this potentially life-saving procedure.

Understanding the Pathogenesis of Refractory Coeliac Disease

Recent advances in understanding the pathogenesis of refractory coeliac disease (RCD) have brought scientists closer to developing targeted treatments for this condition. Current treatments leave many patients with on-going symptoms and some at risk of developing a form of cancer with a poor prognosis.

At a press conference on 15th October, Dr. Georgia Malamut from Paris Descartes University, and a UEG Rising Star discussed several lines of basic research which are currently being explored for the treatment and possible cure of RCD.

"Now we know there are two distinctly different forms of RCD, and we are beginning to understand their underlying mechanisms, which is the first step towards more targeted treatments for this condition", said Dr. Malamut. Dr. Malamut explained that type 1 RCD resembles uncomplicated active coeliac disease and probably results from self perpetuated inflammation due to autoimmunity, while type 2 RCD resembles a low-grade lymphoma, with the accumulation of abnormal lymphocytes (white blood cells) in the lining of the intestine. Current treatment options for RCD type 1 include steroids and immunosuppressive drugs. These improve symptoms, but do little to alter the underlying pathology and can be associated with unpleasant side-effects. The poor prognosis associated with RCD type 2 has led to more aggressive treatment approaches, including chemotherapy. Stem cell transplantation and combined chemotherapy plus stem cell transplantation are under clinical investigation.

Dr. Malamut believes that developing better treatments for RCD will rely on identifying the mechanisms underlying these conditions. She said great progress had recently been made in determining why abnormal lymphocytes accumulated in the intestine, pointing to a defect in the mechanisms associated with normal lymphocyte cell death. "Recent evidence suggests that the cytokine interleukin 15 (IL-15) may be involved in the build-up of these abnormal lymphocytes in patients with RCD type 2," she explained. "Blocking IL-15 using antibodies is a promising therapeutic approach that needs further evaluation."

"In the future, the treatment of patients with RCD type 2 will probably involve a combination of conventional chemotherapy and targeted treatments such as IL-15 antibodies," said Dr. Malamut.

Beware the Hidden Enemy

Prof. Matthias Löhr from the Karolinska Institute, Sweden presented a symposium which encouraged doctors to consider pancreatitis in heavy drinkers with abdominal pain and diarrhoea. A significant amount of damage needs to occur before abnormalities can be observed, which makes early diagnosis of chronic pancreatitis difficult. An ultrasound scan of the pancreas is usually the first investigation followed by endosonography.

According to Prof. Löhr, symptoms of chronic pancreatitis include persister abdominal pain and loose stools or diarrhoea and possibly weight loss an developing malnutrition because vital dietary nutrients cannot be broke down in the gut and absorbed. Diabetes develops in around one-third of these patients because of a lack of insulin. "Unfortunately, chronic pancreatitis caused by alcohol and nicotine abuse also carries a significant risk of pancreatic cancer, which is one of the deadlie cancers," warned Prof. Löhr. "This makes it essential that we do overlook the possibility of chronic pancreatitis when symptom and that we move quickly to make a definitive diagnosis in or treat and monitor these patients."

Alcohol and smoking cessation are essential in managing the conditio treatment, the use of analgesics and other medications to control the enzyme replacement therapy to improve digestion. Surgery to remo diseased pancreas or clear any blockages may be an option for som

Third ESDO GI Cancer Workshop

The European Society of Digestive Oncology (ESDO) was right in the heart of the action during the 21st UEG Week 2013.

UEG President Prof. Colm O´Morain presented the welcome speach for the 3rd ESDO GI Cancer Workshop in co-operation with the International Digestive Cancer Alliance (IDCA) and the European Society of Gastrointestinal Endoscopy (ESGE).

This workshop was held on the 12-13 October during UEG Week. Speaking about the event, Prof. O´Morain said: "In Gastroenterology, we have to work as a multidisciplinary team and I think that ESDO is a great example of that." He said "I think the term united is also underlying this symposium, which is a joint initiative between IDCA, ESGE and ESDO. So I think that we could not be more united with the common goal of improving the output that happens to individuals who put their trust in us."

This fantastic workshop gave a comprehensive overview of Innovation in GI Cancer: From screening to personalized medicine. The event was hosted over two days, with each day focusing on a different theme. On Saturday the workshop's focus was 'The role of screening in GI cancer', which took a closer look at how screening can be ultised in the treatment of GI cancer. On Sunday the workshop's focus was 'From pathways/ targets to personalized medicine', which explored the transition from diagnosis to providing a more personalised care path.

For the first time, all lectures given in these workshop were recorded and featured on UEG e-learning, the universal source of knowledge in gastroenterology.

For more information visit www.esdo.eu

Ohmega - For Complete Reflux Measurement

Medical Measurements Systems were showcasing the Ohmega, a device that makes acidic and non-acidic esophageal reflux detection simple. Providing comprehensive reflux measurement, with this device data recordings can be viewed online through Bluetooth

Complete Reflux Measurement

The Ohmega is a small and lightweight ambulatory system which combines Impedance recording and pH recording. As a result, the Ohmega detects reflux activity using Impedance and categorises these reflux episodes as acidic or non-acidic (weakly acidic), using traditional pH measurement. Gas and mixed liquid/gas reflux episodes are also analysed.

The Virtual Instructor Program™ helps to complete the procedure successfully with minimal training. Bluetooth® capabilities make it possible to view and check data on a computer monitor while recording. The intelligent symptom analysis software quantifies reflux episodes quickly and simply.

Gastro-Esophageal Reflux Disease (GERD) is caused by the reflux of gastric contents into the esophagus. Typical patient symptoms are heartburn, regurgitation, and chest pain. These patient groups are often on PPI medication, but non-acidic reflux can still cause symptoms. Traditional pH recording only records acidic pH reflux episodes, whereas Impedance-pH detects both acidic and non-acidic reflux episodes.

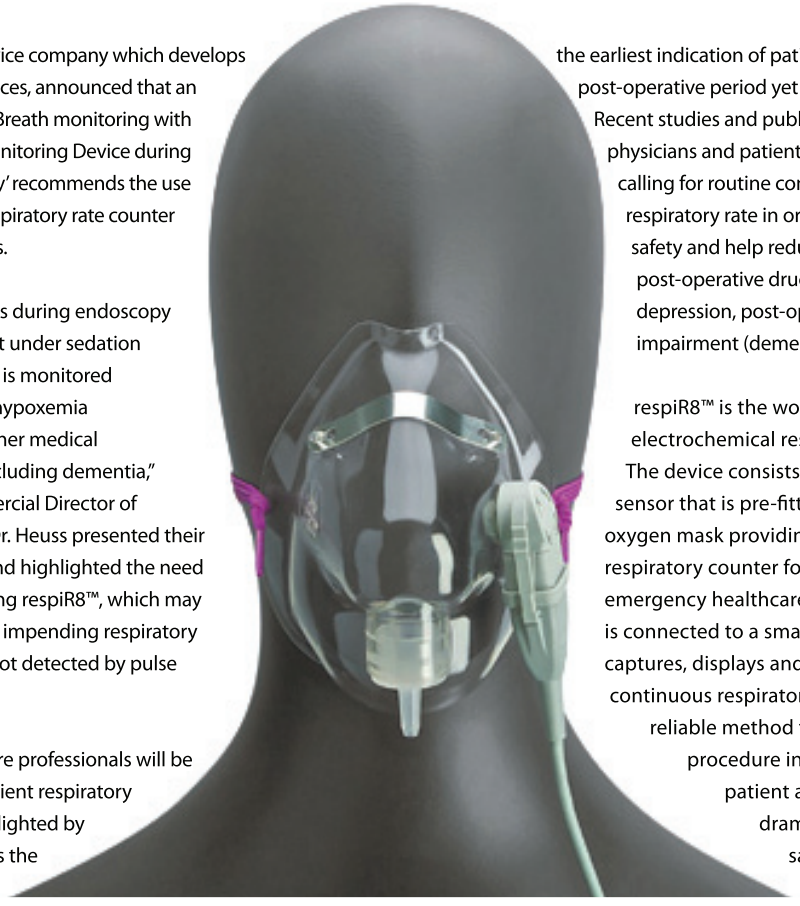
Combined Impedance-pH recording is clinically useful in the evaluation of symptoms under PPI therapy, as well as for hoarseness, unexplained cough, and applications of particular interest.

respiR8™ Recommended for Continuous Respiratory Rate Counter

Anaxsys Ltd, a medical device company which develops innovative respiratory devices, announced that an independent Swiss study 'Breath monitoring with a new Respiratory Rate Monitoring Device during Colonoscopy : A pilot study' recommends the use of respiR8™ continuous respiratory rate counter in colonoscopy procedures.

"Apnoea commonly occurs during endoscopy and operations carried out under sedation and unless the ventilation is monitored continuously can lead to hypoxemia and increase the risk of other medical complications later on, including dementia," said Barbara Lead, Commercial Director of Anaxsys. "Dr. Anand and Dr. Heuss presented their poster at the UEG Week and highlighted the need to monitor ventilation using respiR8™, which may provide earlier warning of impending respiratory abnormalities which are not detected by pulse oximetry alone."

"Using respiR8™, healthcare professionals will be able to better monitor patient respiratory rate, which has been highlighted by the medical community as the vital sign which provides the earliest indication of patient deterioration in the post-operative period yet is the least monitored. Recent studies and publications by eminent physicians and patient safety organisations are calling for routine continuous monitoring of respiratory rate in order to improve patient safety and help reduce the incidence of post-operative drug induced respiratory depression, post-operative cognitive impairment (dementia) and cardiac arrests."



respiR8™ is the world's first continuous electrochemical respiratory rate counter. The device consists of a novel patented sensor that is pre-fitted into a standard oxygen mask providing a very accurate respiratory counter for doctors, nurses and emergency healthcare professionals. The mask is connected to a small electronic monitor that captures, displays and records the patients' continuous respiratory rate. respir8™ is a reliable method for this crucial monitoring procedure in the awake or sedated patient and has the potential to dramatically improve patient safety and considerably post anaesthetic risks.

Evolution of Capsule Endoscopy

Capsovision's stand was visited by many international medical professionals to learn more about the new standard in capsule endoscopy, the CapsoCam SV-1

The innovative new technologies embedded in CapsoCam SV-1 aims to empower gastroenterologists and their teams to achieve significantly better clinical outcomes and improving theirs and their patient's quality of life and at the same time providing economical and affordable solutions.

Capsule endoscopy has evolved over the last decade to become the gold standard for non-invasive diagnosis of small-bowel pathologies. Ongoing research and clinical evaluations continue to expand the range of clinical indications. However, capsule endoscopes themselves have only improved incrementally—until now.

CapsoCam SV-1 is a truly innovative capsule endoscope for visualising the small bowel. The CapsoCam SV-1 employs four cameras facing the sides of the capsule that together image a full 360° about the capsule's circumference and capture high-resolution images of the mucosa including surfaces hidden behind folds. The CapsoCam captures 20 frames per second for the first two hours at a rate of 5 frames per second per camera and thereafter 12 frames per second at a rate of 3 frames per second per camera. The video is more stable due to less camera motion and less mucosal movement.

With the CapsoCam SV-1, there is no generation and transfer of radio-frequency (RF) signals and all the images captured are stored on-board. With CapsoCam, the patient is completely free of any form of external devices and the clinician is freed of the expensive purchasing, deploying and maintaining of receiver equipment and other accessories for data retrieval.

This year CapsoVision held the first ever Partner's Meet, where dedicated distributors presented on their success stories, clinical experiences and feedback from their territories, healthcare market research and product updates.

CapsoVision showed appreciation for the efforts of ABS-Bolton, France and Saesco Medical, Spain and recognised their exceptional efforts in overcoming objections in the field and having a strong pipeline of orders.

The signature Panel Presentation event "The New Standard in Capsule Endoscopy", was the best CapsoVision event to date. It was held at the Kempinski Hotel Bristol Berlin on the evening of Tuesday, 15th October. There were a total of 100 attendees from all across the globe. The event was highlighted by presentations from a panel of international thought leaders that included data on clinical studies and real-life experiences with the CapsoCam SV-1. The presenters included Prof. J.C. Saurin of E. Herriot Hospital, Lyon, France, the lead investigator of the study "Prospective first comparison of an axial and a lateral viewing capsule", who presented on his findings and the benefits of the CapsoCam in his clinical practice. Prof. Dr. Ralf Kiesslich of St. Mary's Hospital, Frankfurt, Germany, detailed his first experiences with the CapsoCam system, concluding that the system is user-friendly for both physician and patient and effective for clinical findings. Dr. Simon Anderson of St. Thomas Hospital, London, UK, discussed the potential of the CapsoCam SV-1 as repeat capsule, an alternative to the traditional forward viewing capsule in negative endoscopic cases, due to the lateral view it provides of the mucosa. Prof. Dr. Miguel Mascarenhas-Saraiva of ManopH in Porto, Portugal, compared the results of capsule endoscopic exams performed with two different systems in 10 patients.

Supporting Surgeons with Tools to Enable an Integrated HD Visual Workflow in 3D

At UEG Week 2013 Sony were present and demonstrated how they were redefining clarity right across today's medical workflow, from prediction and diagnosis to the operating room and beyond.

Sony Medical supports surgeons with the tools and peripherals to enable an integrated HD visual workflow in 3D.

Indeed, the importance of image quality in flexible endoscopy is indisputable. And so are the credentials of Sony Medical in delivering technology that ensures the ultimate image clarity, whilst supporting surgical and post-surgical workflow.

As innovators in the development of HD imaging, Sony offers medical products and solutions that bridge the physical gap between the surgeon and the patient, and they are pivitol in helping improve the quality of diagnosis, intervention and teaching.

3D imaging is becoming an increasingly important tool in today's GI surgical practice. This year, Sony were showcasing their full range of products and solutions that set new standards in 3D and HD imaging clarity for flexible endoscopy.

Medical Grade Monitors and Displays
The newly launched LMD-3251MT is a 32" 3D Full HD medical monitor that features an IPS LCD panel for exceptionally clear, stable colour images plus a wide viewing angle. This high-performance monitor gives a realistic visualisation of complex endoscopic procedures, enabling surgeons to work with greater precision and confidence.

Medical Recorders
The HVO-3000MT video recorder allows surgeons and assistant theatre staff to capture extremely high quality 3D images acquired with any 3D microscopy or endoscopy camera in Full HD.

Medical Printers
The UP-DR80MD is a high-quality, highly durable colour printer for medical applications. Delivering a compelling blend of superior image quality and low ownership costs, it's the world's smallest A4 dye sublimation printer. UP-DR80MD – A4 dye sublimation medical colour printer.

A representative team were available to discuss how users of their devices can deliver more detail and discussed how Sony's end-to-end imaging expertise can support other endoscopy system in HD and 3D.

MediCap USB300 - Affordable High Definition Recorder

Medicapture showcased the MediCap USB300 at UEG Week. This is the medical industry's easiest, most affordable high definition recorder. Users are able to record up to two weeks of HD video on the internal hard drive or record directly to a convenient USB flash drive, and experience easy, affordable HD video without all the hassles of DVD disks.

The MediCap USB300 can record high definition video from your endoscope, arthroscope, surgical camera, ultrasound, etc. It saves this to an internal hard drive or external USB flash drive, which can be accessed via any computer on your network.

With it's steel case and fluid resistant front panel, the USB300 is built to withstand the rigours of the operating theatre, and is so compact it will fit on any cart.

Multiple New Studies Discuss Clinical Benefits of Given Imaging's PillCam® COLON

A world leader in gastrointestinal medical devices and pioneer of capsule endoscopy, Given Imaging Ltd, presented ten abstracts highlighting the clinical utility of PillCam® COLON during UEG Week. Topics ranged from confirming the diagnostic yield of PillCam® COLON and validating feasibility of PillCam® COLON in a general practice setting.

Given Imaging offers healthcare providers a range of innovative options for visualising, diagnosing and monitoring the digestive system. They are committed to delivering breakthrough innovations to the gastrointestinal community and supporting ongoing clinical needs.

"The growing body of data supporting both the clinical accuracy for PillCam COLON and patient preference for a non-invasive, radiation-free colorectal exam strengthen our efforts to expand access to PillCam® COLON in Europe and markets across the globe," said Homi Shamir, President and CEO, Given Imaging.

Some of the highlights of the studies presented at UEG Week include:

- Patients prefer PillCam® COLON because of concern about pain and embarrassment related to colonoscopy.
- PillCam® COLON shows significantly higher diagnostic yield compared to CTC in polyps 6 mm or larger.
- Use of PillCam® COLON following incomplete colonoscopy reveals new lesions in 60% of patients resulting in therapy modifications for 45% of these patients.
- Head-to-head, retrospective comparison of PillCam® COLON versus colonoscopy finds PillCam® COLON generated 90% sensitivity and 96% specificity on a per-lesion basis for detecting flat lesions shown to have a higher risk of being cancerous.

- "French Multicenter Experience of Colon Capsule Endoscopy in Real Practice: Primary Results of the Colon Capsule Endoscopy Observatory 'ONECC'" (poster #1337) was conducted by Jean-Christophe Saurin, M.D., Ph.D., French Society of Digestive Endoscopy and colleagues to analyse survey results from a 161-user, 116-center French database of PillCam® COLON procedures. Survey results from 585 PillCam procedures showed that PillCam® COLON detected polyps in 253 patients, of which, significant polyps were discovered in 125 patients. Researchers also detected significant polyps in 20.4% of patients with previous incomplete colonoscopy, 23.1% of patient contraindicated for colonoscopy and 14.5% of patients who refused colonoscopy. Researchers confirmed the practical application of PillCam® COLON in a general practice setting.

- "Patients Perception of Colonoscopy: Astonishing Reasons for Colon Capsule Endoscopy Preference" (poster #791) validated patient preference for a non-invasive colorectal exam. Researchers from the Department of Gastroenterology and Hepatology at the Institute for Clinical and Experimental Medicine in Prague, Czech Republic led by Marek Benes, M.D. conducted a 100 patient survey analysis to find that 42% of patients reported they will never undergo a screening colonoscopy even though 45% of this subgroup had a positive family history of colorectal cancer. The top reason for preference for PillCam® COLON was due to concerns about privacy and embarrassment experienced with colonoscopy (38%).

- "Flat Colorectal Lesions At Pillcam Colon Capsule Endoscopy" (oral presentation #432) was a comparison of PillCam® COLON versus colonoscopy to evaluate the ability of PillCam® COLON to diagnose flat colonic lesions. Researchers collected data from patients who underwent PillCam COLON followed by a traditional colonoscopy. 27 conventional polyps were identified with colonoscopy and 25 conventional polyps with PillCam COLON. PillCam COLON generated 90% sensitivity and 96% specificity on a per-lesion basis. Researchers concluded that PillCam® COLON has high accuracy for detecting flat lesions.

The utilisation of PillCam COLON following incomplete colonoscopy was highlighted in UEG Week abstracts including: -- "Colon Capsule Endoscopy Versus CT-Colonography in the Evaluation of Patients with Incomplete Traditional Colonoscopy: A Prospective Comparative Trial" (oral presentation #431) presented by Cristiano Spada, M.D., and colleagues from the Catholic University in Rome. Patients in the study underwent both CT-colonography (CTC) and PillCam COLON with the goal of identifying polyps and masses that were at least six millimeters and located in segments of the colon that could not be examined in the previous incomplete colonoscopy. Both PillCam COLON and CTC successfully completed the colonic exam in 98% of patients due to 2% of patients refusing CTC due to air insufflation. Researchers concluded that both exam modalities were effective in completing a colonic exam, however PillCam® COLON had a significantly higher diagnostic yield compared to CTC in identifying polyps six millimeters or larger.

-- "Utility of Colon Capsule Endoscopy After an Incomplete Colonoscopy - Multicenter Spanish Study" (poster #793) led by Oscar Nogales, M.D., Hospital General Universitario Gregorio Maranon, Department of Gastroenterology, Madrid, Spain analysed the use of PillCam COLON 98 patients with previous incomplete colonoscopies. Overall, PillCam® COLON was able to identify new lesions in in 60% of patients. Polyps were the most frequent finding with 41% of patients having a polyp identified by PillCam® COLON. Researchers concluded that Pillam® COLON is a useful diagnostic tool to identify a significant number of lesions in unexplored regions of the colon following incomplete colonoscopy.

Innovative Fuse Gastroscope from EndoChoice

The news that the FDA has granted 510(k) Clearance for EndoChoice® Full Specturm Endoscopy's innovative fuse gastroscopy was welcomed by doctors at UEG Week 2013.

Doctors who perform flexible endoscopy now have a new tool available to help them see more anatomy and facilitate diagnoses in the upper GI tract. Traditional gastroscopes that have so far been available to endoscopists provide a field of view which is limited to about 140 degrees. EndoChoice® announced that the FDA had provided 510(k) clearance of its new Fuse™ Gastroscope, which has a field of view of 245 degrees and they were present at the UEG week to demonstrate their products. EndoChoice's portfolio of Endoscopes include thin flexible tubes with imaging capabilities that doctors can use to view the upper and lower GI tracts of their patients.

EndoChoice engineers have developed a new method of designing and manufacturing flexible circuits that allow them to put more small cameras on the tips of flexible endoscopes. This new concept of Full Spectrum Endoscopy™ is changing the field of endoscopy where significant improvements in technology have not occurred in more than 20 years. The new gastroscope joins the revolutionary endoscopy system line of products released earlier this year by EndoChoice under the Fuse brand. The Fuse Gastroscope has two cameras, and the Fuse Colonoscope has three cameras while traditional systems have just one.

The Fuse system allows doctors to see nearly twice as much surface area as they can with traditional endoscopes. Because of the folds that occur naturally in the colon and stomach anatomy, problem areas can easily go undetected when using traditional endoscopes. The Fuse system allows GI doctors to see into and behind those folds. The images of the anatomy are displayed on high-definition screens specially arranged to give the doctor a full spectrum view.

Data supporting the Fuse system were presented simultaneously at the UEG Week 2013. Researchers demonstrated the ability to see more with the Fuse system, which has a statistically significant impact on their ability to find adenomas or precancerous lesions when compared to traditional single-view endoscopes. "We have a national colorectal cancer screening program in the United States wherein most people should get screened for colorectal cancer, but not all patients follow these guidelines. The data from the Full Spectrum Endoscopy Tandem study would indicate that Fuse is a radical improvement over the tools we've used in the past to fight GI disease," said Douglas K. Rex, Professor of Medicine at Indiana University.

"We are 100% focused on serving the GI professionals so they can give the best possible care to their patients," said Mark Gilreath, Founder and CEO at EndoChoice. "This clearance by the FDA is yet another milestone in our efforts to make the Fuse system available to more hospitals and clinics."

For more information on Fuse™ visit:
www.endochoice.com/fuse

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Did you know that the American Board of Surgery requires 60 Category 1 CME Credits from a self assessment activity every 3 years for Maintenance of Certification (MOC)?

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The Launch of the Next Generation of Endoscopic Ultrasound

Olympus launched its next generation of endoscopic ultrasound during the UEG Week.

Olympus is one of the world's leading manufacturers of innovative optical and digital equipment such as endoscopes and microscopes for medical, scientific and industrial use as well as cameras and voice recorders. This technology leader presented its new ultrasound processor EU- ME2 at the meeting.

The EU- ME2 optimised high-resolution images facilitate the detection and diagnosis of tumours during gastroscopy and bronchoscopy. The quality of the B-mode ultrasound image of the EU-ME2 has greatly improved compared to its predecessor. Furthermore, the processor provides additional functions, such as Tissue Harmonic Echo (THE), Contrast Harmonic Echo (CH-EUS) and Elastography. These serve as a crucial basis for both a precise EUS procedure and a reliable diagnosis.

As with its predecessor, EU-ME2 has been developed especially for endoscopic ultrasound. The new generation of processors fully meets the highest medical requirements with regards to image quality and performance, and its extended functions offer new possibilities for various diagnostic and therapeutic applications. The high quality processor is both compact and fully compatible with all current Olympus endoscopes as well as miniature probes and can be obtained as Standard, Premier and Premier Plus version. The Premier as well as the Premier Plus model are equipped with additional ultrasound technologies apart from the significantly improved B-mode and the standard functions.

The Contrast Harmonic Echo (CH-EUS) mode displays an even more differentiated image of the respective tissue and the blood flow by injecting a contrast medium. This shall allow more precise diagnosis of tumors and other abnormal growths.

Recently, CH-EUS was also co-opted into the recommendations of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB).

Elastography

Sonoelastography displays differences in tissue elasticity in the body on a relative scale. This advanced form of ultrasound aims to aid the distinction between benign and malignant changes of tissue and may help to classify tumours. It evaluates endogenous mechanical impulses such as the deformation caused by the compression or vibrations generated by the heartbeat or vascular pulsations when pressing the transducer softly against the tissue layer. As tumours are usually harder and less elastic than healthy tissue, thus anomalies can be analysed.

Tissue Harmonic Echo (THE)

An important additional function is THE. The harmonic imaging mode improves the signal-to noise ratio, reduces artifacts and enhances the precise depiction of tissue boundaries.

High Resolution Flow (H-Flow)

This is especially useful for imaging small vessels is the H-Flow mode. It can facilitate more precise maneuvering of the instruments during fine-needle aspiration (FNA) and sonographic transbronchial needle aspiration (EBUS-TBNA) by making it potentially less difficult to avoid vessels.

Pulse Wave Doppler (PWD) and FLOW Mode

The PWD and the FLOW mode provide fundamental information about the area to be examined, such as blood flow velocities and quantity of blood.

Comprehensive Portfolio

Offering a significantly improved image reproduction and enhanced functions the new Olympus EU-ME2 reaches a high standard in the field of endoscopic ultrasound processors. For EUS applications the EU-ME2 joins the ranks of the high quality processor range, also including the Hitachi/Aloka prosound F75 and prosound α7 distributed by Olympus - which beside endoscopc ultrasound, also offer the possibility to attach abdominal probes. Olympus offers a high quality and comprehensive product portfolio that fulfills the different needs in sonography.

For more information visit:
www.olympus-europa.com/medical

novoGI™ HemoDetect System

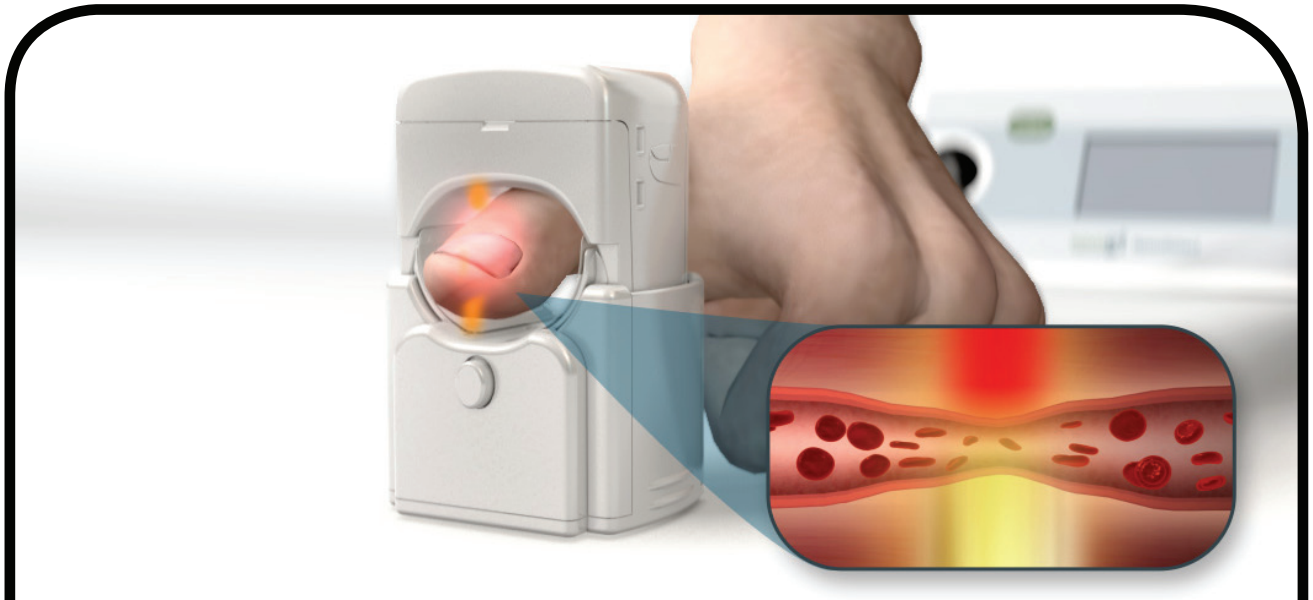
novoGI™ is committed to advancing patient care through providing an expanding range of solutions for GI disease management. This year at UEG Week they were demonstrating the novoGI™ HemoDetect system. The novoGI™ HemoDetect test is a clinically proven non-invasive Haemoglobin measurement desktop device. The technology combines sensitive optical measurement with temporary blood-flow occlusion using a pneumatic thumb sensor cuff.

A ring-shaped sensor probe is placed on the patient's thumb, and the sensor ring automatically applies gentle pressure, creating temporary occlusion of blood flow in the finger.

During the test new blood dynamics are created, generating a unique, strong optical transmission signal. The device has a high signal-to-noise ratio, enabling highly sensitive measurements of Haemoglobin level. Optical elements in the sensor measure the light transmitted through the finger. The results are then calculated immediately and Haemoglobin level is shown in an easily readable output mode on a portable and compact monitor.

The HemoDetect test was evaluated and tested on over 10,000 cases in Europe, U.S, Latin America and Asia. It exhibits accuracy comparable to invasive point of care solutions while demonstrating clear superiority in safety, cost effectiveness, immediate results and ease of use.

In a recent study findings indicated that Hb measurements using HemoDetect are accurate when compared to measurements with the gold standard invasive devices.



Epi proColon® Nerve Stimulation System

Inspire Medical Systems Inc., showcased their nerve stimulation systems at the show. This device is most effective for a subset of patients who have a certain type of soft-palate collapse and are not significantly obese. It is designed to significantly reduce the burden of obstructive sleep apnoea by delivering mild stimulation to the upper airway during sleep.

A small, fully implantable system this utilises electronic stimulation therapy to reduce obstructive sleep apnoea (OSA).

Inspire's implantable Upper Airway Stimulation (UAS) Therapy is a promising treatment for moderate to severe OSA in patients who do not respond to or can not tolerate continuous positive airway pressure (CPAP) therapy.

Inspire therapy is designed to deliver physiologically-timed, mild stimulation to the main nerve of the tongue on each breathing cycle during sleep in order to restore tone to key airway muscles and prevent airway collapse. The stimulation is sufficient enough to evoke a response from the nerve but mild enough not to disturb sleep.

Patient's control when the Inspire therapy is turned on and off using a handheld controller. The pulse generator processes information from the sensor and determines the most beneficial time in the breathing cycle to deliver the stimulation. The single lead pressure sensor provides real-time breathing cycle data throughout the night.

In contrast to other surgical procedures which treat sleep apnoea, Inspire therapy does not require removing or altering a patient's facial or airway anatomy.

"The device's battery is expected to last between eight and 10 years", says Randy Ban, Senior Vice President, External Operations.

Potent and Selective Inhibition of FFA2

Galapagos presented *in vitro* and Phase 1 data showing potent and selective inhibition of FFA2 by GLPG0974 at the UEG Week.

"The FFA2 antagonist GLPG0974: Opportunity to treat neutrophil-driven inflammation" was presented on 16th October and awarded as the Poster of Excellence designation from the UEG Week Scientific Committee.

FFA2 (free fatty acid receptor 2) has been shown to play a role in neutrophil migration. Over activity of neutrophils is caused when there is tissue damage in illnesses such as inflammatory bowel disease. The poster provided *in vitro* pharmacology supporting that GLPG0974 is a potent and selective antagonist of FFA2, and favorable Phase I pharmacokinetic, pharmacodynamic, and safety data with GLPG0974.

Taken orally GLPG0974 is small molecule that reduces migration of neutrophils, one of the critical cell types in inflammatory processes, by potent inhibition of FFA2 (also known as GPR43).

Over-activity of neutrophils is a cause of tissue damage in illnesses such as inflammatory bowel disease. A reduction of neutrophil activation and migration by inhibition of FFA2 may provide for a novel anti-inflammatory treatment approach. By inhibiting FFA2, GLPG0974 prevents free fatty acid-induced activation and migration of neutrophils towards an inflammatory site, such as in the gut of patients with inflammatory bowel disease. GLPG0974 is the first inhibitor of FFA2 to be evaluated clinically. Galapagos expects to report results of the Proof of Concept study in ulcerative colitis in early 2014.

VSL#3 Now Supported by Scientific Data

Two posters were presented on VSL#3 at the UEG Week this year. The first poster was displayed on the Tuesday 15th October and was titled 'Effect of a Probiotic preparation (VSL#3) in the patients with ulcerative colitis: its effect on cytokines'.

On Wednesday 15th October the second poster titled 'Open label, randomized international multicenter study of the impact of diet on, inflamm-ageing, Oxidative stress and gut microbiota in elderly people (Ristomed): benefits of dietry advice alone or in conjunction with VSL#3® probiotic' was displayed.

VSL#3 is one of the few probiotic preparations supported by Level One (double-blind, placebo-controlled) scientific data. VSL#3 has been the subject of extensive clinical research in the dietary management of ulcerative colitis, irritable bowel syndrome, an ileal pouch, and several other clinical conditions.

Increasing evidence shows that the activity of probiotic bacteria in the human GI tract plays a role in the dietary management of certain diseases. The intestine is colonised by more than 400 different bacterial species. 40 of these are predominant and are made of aerobic and anaerobic bacteria, both Gram-positive and Gram-negative, such as the bacteria listed to the right.

In the colon, bacteria reach a concentration of 1010 - 1012 per ml of faecal contents. It has now been scientifically proven that the intestinal microflora, and in particular Bifidobacteria and Lactobacilli, play a significant role in the:

- Reduction of the intraluminal pH through the production of lactic acid, acetic acid and other organic acids;
- Production of nutrients (short chain fatty acids, arginine, glutathione, vitamins, etc.) necessary for correct functioning of the intestinal mucosa;
- Competition with pathogenic microorganisms for nutrients and for adhesion to the intestinal epithelium;
-Production of bacteriocins.

The intestinal microflora play a significant role in metabolic function both from a nutritional point of view as well as for the maintenance of an efficient intestinal mucosal barrier.

Xtend Breath Test Monitor

Lactotest 202 has been developed to provide quick and reliable diagnosis of gastrointestinal disorders measuring carbohydrate breakdown deficiencies and/or malabsorption. Particularly efficient for lactose intolerance screening, the instrument also gives a good indication of excessive bacterial growth in the gut and evaluates intestinal transit time. The electrochemical sensor with thermal compensation for hydrogen and infra-red analysers for methane and carbon dioxide deliver a reliable, rapid and inexpensive system of measurement.

Hydrogen (H2) is produced in the intestinal lumen by bacteriological breakdown of carbohydrates. However, many studies have shown that approximately 30% of patients may also produce methane (CH4)*. Detection of both gases is therefore complementary and helps clinicians to under- stand digestive problems.

It is also important to measure carbon dioxide concentration (CO2) in the breath to determine whether the breath samples for analysis are alveolar, otherwise results are underestimated.

The technique of exhaled breath hydrogen monitoring is normally well tolerated by patients of all ages. The test is simple, non-invasive and it is performed after a short period of fasting. Ease of use, clinically proven technique and cost effectiveness make that the Lactotest 202 "Xtend" is becoming a standard diagnostic tool for gastroenterologists, paediatricians and clinical biochemists.
All lactotests are interactive systems.
USB communication allows you to interface with adapted PC software for database integration, o export results to Hospital Informatics System (XML, HL7, etc.) or simply to print directly results in MS Word™ in order to have an automatic addition of these results in the patient data file.

International Survey Demonstrates Constipation's Substantially Impact On Patients' Quality Of Life

On Wednesday 16th October, 2013 an international market research survey,[1] funded by Norgine, was presented at the UEG Week in Berlin. The survey, in which 766 patients were drawn from nine European countries, Australia and South Africa, showed that constipation is a common condition which has a major impact on patients' lives. All patients participating in the survey were required to have taken either prescribed or over-the-counter laxatives in the previous year. Ninety-eight percent of these patients said that living with chronic constipation negatively affected their quality of life.[1]

The survey also demonstrated how constipation impacts on their ability to lead a normal life, for example:[1]

- Almost one-third of sufferers feel their concentration at work is affected by their condition.
- More than half feel their diet is affected.
- Almost one-third feel their social life is affected as a result of the condition.
- Over one-third experienced disturbed sleep because of their constipation.

Contrary to popular perceptions, constipation is not a mild or transient illness according to those participating in the survey. Almost one-fifth of constipation sufferers reported that they live with severe constipation (with faecal impaction) and just over one-third suffer moderate but persistent constipation.[1] More than three-quarters of those surveyed had experienced constipation for over six months and 41 percent had lived with constipation for over five years.[1]

Over half of those surveyed felt "irritated" by their constipation, with others describing themselves as "embarrassed", "stressed" and "concerned" as a result of living with the illness.[1]

Responses suggest that patients wanted laxative treatments that worked well and quickly, with limited side-effects.[1] While patients are using a variety of commonly-available laxative treatments to try to manage their constipation, it is not always clear why one treatment option is chosen over another. For example, around two-thirds of those patients taking PEG+electrolytes reported that they only took the medicine when they had symptoms and 60% took one sachet or less per day.[1] One-third of patients surveyed had been taking their current laxative treatment for more than one year.[1] The most common reason for choosing to switch treatments was a perceived lack of, or reduction in, efficacy, followed by doctors' recommendations and side-effects.[1]

"These data clearly show that constipation is a common gastrointestinal disorder which is often chronic, can last for extended periods of time and has a substantial impact on patients' quality of life," commented Dr. Pauline Jouët of Hôpital Louis Mourier, France and co- presenter of the UEGW abstract. "Doctors have an important role in advising sufferers how to manage this condition and laxative choice as it is clear from these results that there is still a considerable need for proactive medical support for these patients."

"These data clearly show that constipation is a common gastrointestinal disorder which is often chronic, can last for extended periods of time and has a substantial impact on patients' quality of life," Dr Pauline Jouët of Hôpital Louis Mourier, France and co- presenter of the UEGW abstract.

Constipation is a common gastrointestinal disorder which is often chronic and associated with an impaired quality of life (QoL).[2] Laxatives are a treatment of choice after failure of lifestyle and dietary changes.[3] However different laxatives can be used and factors affecting the choice of laxative are poorly studied.[4] The objective of this survey was to assess the characteristics of the patients' constipation, impact on QoL and factors associated with laxative choice.

For more information visit www.norgine.com

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TRUD™ The Latest Treatment for Ulcerative Colitis Patients

Ulcerative colitis is a disease of the colon and rectum in which the mucosal lining becomes inflamed. Symptoms include rectal bleeding, frequent diarrhoea and abdominal pain. One of the latest treatments offered for mild to moderate Ulcerative Colitis (UC), TRUD™ was exhibited at UEGW.

TRUD™ is applied via the rectum and forms a protective coat over the lining of the distal colon and rectum. This allows the mucosal tissue to heal naturally, which reduces the symptoms of ulcerative colitis.

TRUD™ is intended to be used to supplement the intestinal mucosa of patients suffering from mild to moderate distal ulcerative colitis. TRUD™ provides a soft barrier to minimise the effects of continuous immune stimulation by triggers from the contents of the colon on the colonic mucosa and thereby provide the ideal environment for the regeneration of the intestinal mucosa.

TRUD™ contains 2 different specific types of Sodium Hyaluronate (also known as Hyaluronic Acid, or Hyaluronan) as well as a natural muco-adhesive agent, which ensures that Sodium Hyaluronate adheres to the mucosa for a longer period. There are two important properties, specific to the size of the Sodium Hyaluronate which could explain why TRUD™ has shown effectiveness in treating patients with mild to moderate UC. These include facilitate healing and protection.

The low molecular weight Sodium Hyaluronate that can be found in TRUD™ is able to help improve the healing rate of the affected region (in the colon). The small sized Sodium Hyaluronate molecules promote the rate of healing at the muscosal level which is affected by UC, a process called epithelial restitution.

The high molecular weight (large sized) Sodium Hyaluronate together with the muco-adhesive agent (Xanthan gum) is able to adhere specifically to where the colon is affected and protect this inflamed and ulcerated area whilst the healing is taking place. This is important as the colon contains a lot of bacteria and toxins which could be accidentally absorbed in the ulcerated area or, could cause further inflammation.

TRUD™ was registered for sale in Europe in April 2013 after its safety and effectiveness for the treatment of mild to moderate UC was demonstrated in a clinical study conducted in Istituto Clinico Humanitas, (Milan) Italy.

Almost a quarter of the patients in the study showed complete mucosal healing in the colon demonstrating that TRUD™ is effective in facilitating the healing of the affected colon of patients with mild to moderate UC in the acute phase.

No serious adverse events were seen in any patient during the course of the trial. Some mild transient side effects (e.g. flatulence, nausea, headache, etc.) were seen which could be due to the procedure of using an enema.

TRUD™ was found to be well tolerated as a form of treatment for patients with mild to moderate UC.

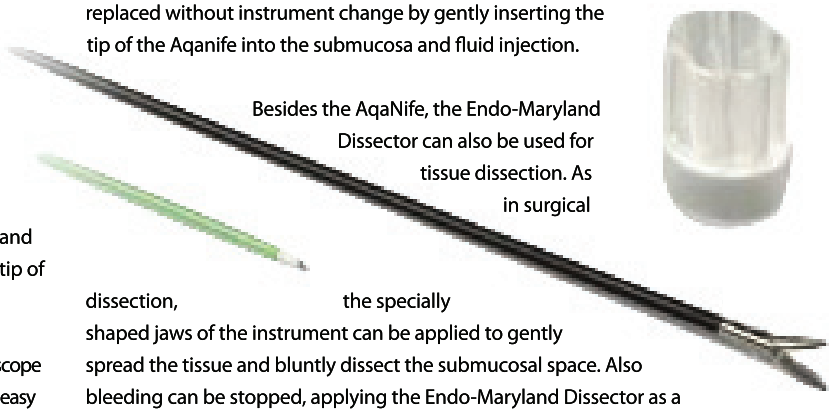
Endoscopic Submucosal Dissection

Ovesco Endoscopy were demonstrating the AqaNife at UEG Week. The AqaNife is used for Endoscopic Submucosal Dissection, which consists of several steps. The first is usually the placement of coagulation marks around the lesion with a safety margin. This facilitates identification of the resection margin during the procedure.

The next step is sumucosal liquid injection to lift the mucosa from the muscular layer. Then follows the incision of the mucosa and the subsequent HF-dissection of the submucosal space with the tip of the AqaNife.

The VersaCap, Ovesco's new ESD cap, adapts flexibly to a range of endoscope diameters. Its soft material makes introduction and tissue manipulation easy and it supports access to the submucosal space for dissection.

Lost fluid, occurring during dissection over time, can be replaced without instrument change by gently inserting the tip of the Aqanife into the submucosa and fluid injection.



Besides the AqaNife, the Endo-Maryland Dissector can also be used for tissue dissection. As in surgical dissection, the specially shaped jaws of the instrument can be applied to gently spread the tissue and bluntly dissect the submucosal space. Also bleeding can be stopped, applying the Endo-Maryland Dissector as a coagulation grasper.

Probiotics - The Key to Encouraging the Completion of Antibiotics?

Better education is key to reduce 'frightening' levels of drug wastage.

A study of UK doctors carried out by the PCSG (Primary Care Society for Gastroenterology) to coincide with European Antibiotics Awareness Day on18th November 2013 has suggested that patients who are given information about the impact of antibiotics on the gut and the option of probiotics before being prescribed antibiotics are far more likely to complete the full course.

Probiotics are increasingly recognised as giving a helping hand to the gut microbiota - the colonies of friendly bacteria that we all have inside us, and that can be disrupted by taking antibiotics.

Doctors quizzed in the survey say that at least half of patients who are told about the workings of gut microbiota and how probiotics may help are likely to complete a course of antibiotics, compared with just a third of patients who are not given this information by their GPs. The survey also showed that, like their patients, doctors are also becoming more aware of the advantages of probiotics. A third now consider the possible impact of antibiotics on gut microbiota when writing prescriptions.

Around over six in every hundred people are prescribed at least one course of antibiotics every year. Yet as many as sixty percent give up on them half way through, according to many of the doctors quizzed in the survey. Indeed, just five out of a hundred doctors surveyed were optimistic that three quarters of their patients would finish their medicine. Perhaps more unnerving still, GPs thought 80% compliance is the best that it gets. No GP believed that more than this figure would keep on taking the medicine.

On a national scale, that could add up to as many as two million courses of antibiotics never being completed, leading to massive waste and the growing problem of antibiotic resistance.

'If talking to patients about the benefits of probiotics will encourage them to finish their courses of antibiotics, it has to be good news,' says Dr. Patricia McNair, a PCSG member and GP from Sussex. 'This research points to the importance of patient knowledge and education in helping to deal with what is likely to become one of the biggest health issues of our time.'

The study was funded by Danone Ltd through an unrestricted educational grant that had no influence on the results.

Research was carried out amongst 120 GPs in October 2013. Of these, 24% were in the south east, 9% in Scotland, 10% in the north west, 30% in the north east, 15% in the Midlands, 8% in the south west and 4% in Wales.

The PCSG is the voice of gastroenterology in primary care. The society was launched in 1985 and has forged strong links with several organisations both nationally and internationally. Bodies such as the British Society of Gastroenterology, the Royal College of Physicians, NICE, and the RCGP all consult the PCSG regularly on gastroenterological subjects so that policies and guidelines can be influenced by primary care. To find out more, please visit www.pcsg.org.uk.

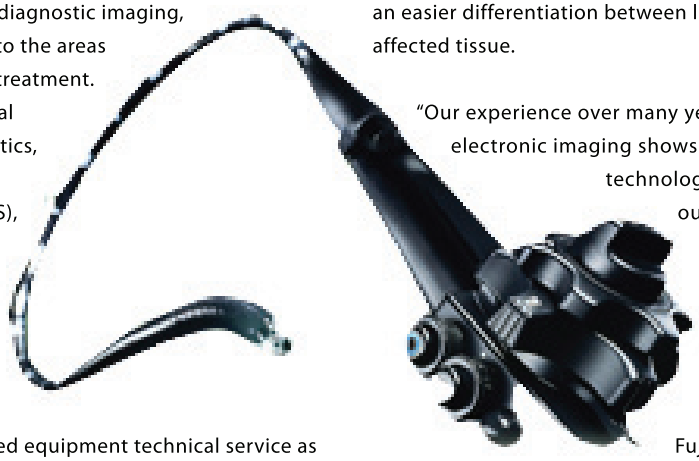
European Antibiotics Awareness Day is an annual European public health initiative that takes place on 18th November to raise awareness about the threat to public health of antibiotic resistance and prudent antibiotic use. The latest data confirms that across the European Union the number of patients infected by resistant bacteria is increasing and that antibiotic resistance is a major threat to public health.

Prudent use of antibiotics can help stop resistant bacteria from developing and help keep antibiotics effective for the use of future generations.

World Premiere for CMOS Image Sensor

The Endoscopy Division of FUJIFILM Medical Systems Europe showcased a number of advances at UEG Week. The company displayed a line-up of new products and hosted lectures on the latest technological advances.

Fujifilm is a pioneer in digital diagnostic imaging, which is rapidly expanding into the areas of preventive healthcare and treatment. The portfolio consists of Digital Imaging solutions for diagnostics, medical picture archiving and communication systems (PACS), computed radiography, digital radiography, digital mammography, dry imagers, x-ray film and screen, endoscopy systems, clinical chemistry analysers, ultrasound systems, and related equipment technical service as well as technical application support.



Fujifilm has used the over-megapixel customised CMOS sensor in the new gastroscopy and colonoscopy systems EG-600WR and EC-600WM/WI/WL series. By adapting a CMOS image sensor, the new 600 series endoscopes enable super-high resolution images to be produced. The leading CMOS technology realises less noise and brilliant images by converting the analogue signal to digital in the tip of the scope. During transmission the digital signal is significantly less affected by any noise from the outside. CMOS Technology also realises 60 frame progressive video.

By adopting ColoAssist II in EC-600WM/WI/WL both force and torque transmissions have been improved. Compared to the previous type, gradual stiffness level has been adjusted: it is softer at the distal and harder at operating side, resulting in more efficient transmission.

The focus at the edges of an image has been improved, minimising distortion in observation of a lumen. Through a combination with the megapixel CMOS image sensor, high performance optical system assists various observations ranging from close-up to distant views. Through higher resolution and improved noise reduction, FICE images are far sharper and clearer than ever. It enables an easier differentiation between lesion-affected and non-affected tissue.

"Our experience over many years in optoelectronics and electronic imaging shows the superior quality of this technology and we can expect that our customers will see the difference instantly" says Kazuhiko Takemura, Head of European Endoscope Department, FUJIFILM Europe.

Fujifilm were also displaying the new Double Balloon Endoscope EN-580T which has now added been added to their portfolio of double-balloon endoscopes. This has greatly contributed to precise diagnosis and treatment for diseases of the small intestine. A large forceps channel of 3.2 mm provides greater suction performance. The integrated Super CCD sensor ensures vivid and high quality images. Used in combination with FICE the EN-580T enables easier differentiation between lesion-affected and non-affected areas. A newly designed one-touch connector and relocated balloon air feed inlet provides for better operability.

In addition to the product showcased at the booth, Fujifilm also hosted a Symposium on 14th October under the title 'New horizons in GI screening and therapeutic endoscopy'.

For more information, please visit: www.fujifilm.eu/medical.

Microscopic Colitis – New Insights in an Emerging Disease - Interview with Prof. Dr. Stephan Miehlke, Hamburg

Christine Vetter speaks with Prof. Dr. Stephan Miehlke, Co-chair of the Falk Evening Symposium 'Microscopic Colitis – New Insights in an Emerging Disease' to find out more about this disease and the treatments available to combat it.

Prof. Miehlke, is microscopic colitis really a relevant disease or is it more a passing fashion?

This topic is not trivial and is certainly not a passing fashion. Microscopic colitis is in fact a relevant disease, although its importance has been underestimated for a long time. The fact that microscopic colitis has now been recognised by the ECCO as a chronic inflammatory bowel disease demonstrates that this is changing nationally and internationally, and that the significance of the disease is becoming better understood. In the most recently published consensus-based guidelines on the histopathology of chronic inflammatory bowel disease, microscopic colitis has been recorded as an entity in its own right. In my view, there is now no longer any doubt that the disease is a chronic inflammatory bowel disease along with ulcerative colitis and Crohn's disease. Microscopic colitis is detectable using clear pathophysiological parameters and causes symptoms that can be clearly attributed to it. Patients suffer from considerable distress and benefit from well-designed treatment.

Can you describe the course of the disease?

In most cases, microscopic colitis is a chronic disease. The overwhelming majority of patients respond to drug treatment but symptoms recur quickly in 80% of patients when the medication is discontinued.

When should microscopic colitis be considered in medical practice?

The main symptom is watery non-bloody diarrhoea, so you must always be alert if a patient reports having nocturnal diarrhoea. Women are much more frequently affected than men and the onset of the disease is mostly in the fifth to sixth decade of life. In women of this age, microscopic colitis should therefore always be considered if they present in medical practice with persistent watery diarrhoea. But despite this, it should not be forgotten when you are faced with symptoms of this kind that men and young adults can also suffer from the disease.

What investigations should be launched following a suspected diagnosis?

A full colonoscopy with multiple colonic biopsies should be performed, and it is essential that the proximal colon also be included. Otherwise, the disease will be missed in 30-40% of cases. There are few or no endoscopic abnormalities. Microscopic colitis can only be established definitively by biopsy and histology.

What forms of the disease are there?

We differentiate between collagenous and lymphocytic colitis, which have distinct histological pictures. There is a third, so far little known form of the disease known as incomplete colitis. Patients affected by it suffer characteristic symptoms. Pathologists describe a chronic inflammatory response in the lamina propria, as with microscopic colitis. But, in this case, the number of intraepithelial lymphocytes is lower than the diagnostic cut-off (which is, admittedly, arbitrary). This is clearly a third form of disease: in fact, incomplete microscopic colitis is also histologically distinguishable from the collagenous and lymphocytic types.

Are the various forms of the disease of any significance for prognosis?

The clinical course of the histological subtypes is very similar, but appears to be somewhat milder in lymphocytic colitis and incomplete MC. The overall prognosis of effectively treated patients is good since MC is not associated with colonic cancer, polyps or any structural damage.

What is the procedure for treatment?

The treatment of choice for collagenous colitis is budesonide, which is also approved for short-term therapy. Treatment lasts 8 weeks at 9 mg per day. The active substance has not yet been approved for use in treating lymphocytic colitis but there are already 2 controlled studies that document that the local steroid has good clinical effectiveness in this disease too. For incomplete colitis, there are still no study data, but a controlled study is currently being run led by the European study group. However, there are retrospective data from a Danish cohort that provide evidence of good response to budesonide in cases of incomplete colitis too.

What is the procedure for patients in whom the disease recurs?

In our experience, the majority of patients do in fact require long-term therapy. In our view, maintenance treatment is then indicated at a lower dosage of budesonide. There have already been 2 studies into this question, in which budesonide was administered at a dosage of 6 mg daily for 6 months. This enabled 75% of patients to maintain remission. The BUC-63 study further showed that in around 60% of patients with collagenous colitis who achieve remission under treatment with budesonide, remission can also be maintained for a year simply through treatment with 4.5 mg of the active substance.

What action is still required on microscopic colitis?

Quite apart from the fact that we so far have no treatment option that is officially approved for long-term treatment, we also have no treatment alternatives to budesonide for patients who do not respond to the active substance, are intolerant of it or for whom it is contra-indicated.

EMCG
EUROPEAN MICROSCOPIC COLITIS GROUP

Symposia Highlights

'IBS-C, A Complex Disease Area: Are we doing the Best for our Patients?

Prof. Peter Layer and colleagues from Almirall invited attendees of UEG Week to attend their symposium entitled 'IBS-C, a complex disease area: Are we doing the best for our patients?'

Prof. Layer chaired the symosium and began with the opening welcome and introduction lecture.

He explanied that the symposium's aim was to bring together esteemed experts, who would discuss the challenges of diagnosing and treating IBS, recent advances in managing IBS-C, and how we can optimise patient care.

Peter Whorwell and Viola Andresen began the session with an interactive case study session looking at practical issues in diagnosing IBS-C, including patient needs, physician attitudes, and data from a recent online survey of European primary care physicians, gastroenterologists and IBS experts.

Fermín Mearin and the team then discussed symptom-based positive diagnosis using Rome criteria and how this can aid the accurate diagnosis of IBS and eliminate unnecessary interventions. They also explored if and how these criteria can fit into daily clinical practice.

An update on the enormous progress achieved in understanding pathophysiological mechanisms of IBS was given by Giovanni Barbara. In his talk entitled 'IBS pathophysiology: What do we know?' he also looked at how these mechanisms interact to manifest as symptoms, and how a better insight into IBS pathophysiology may aid new treatment development was also given.

Last but not least, Jan Tack gave a talk on 'Managing multiple symptoms: A new treatment option for IBS-C'.

Finally, the team concluded with a new treatment option for IBS-C, with a novel mode of action, that can achieve multiple symptom relief, and examined how and where this new option may fit into the traditional IBS-C armamentarium.

Innovations in Targeted Therapies for Inflammatory Bowel Disease: Evolving Paradigms and Optimising Outcomes

On Sunday 13th October Prof. Stefan Schreiber chaired the Takeda symposium entitled 'Innovations in targeted therapies for inflammatory bowel disease: evolving paradigms and optimising outcomes'. This was an opportunity for gastroenterologists from across Europe to discuss evidence and data around targeted therapies in inflammatory bowel disease (IBD).

This symposium provided a unique opportunity to discuss the clinical challenges and current unmet needs in IBD; to identify the similarities and differences in management challenges between ulcerative colitis (UC) and Crohn's disease (CD); and explore current areas of focus, including assessing new mechanisms to control intestinal inflammation, treating patients beyond symptom control and concerns regarding the risk of long-term systemic immune suppression.

The team examined the current burden of IBD to patients and society, define what we mean by targeted therapy, and highlight what the current unmet needs are with regards to long-term efficacy and safety.

Dr. James Lindsay presented a detailed look at how to optimise available treatment strategies. He looked at the difficulties in achieving and maintaining response with currently available therapies, and the need for therapeutic drug monitoring. He discussed the challenges around switching between anti-TNFs, and the options available for more targeted therapies.

Prof. Remo Panaccione looked at how new biological agents are expanding the armamentarium for the treatment of IBD. This involved an exploration of what targeted drugs are available or are in advanced stages of development for IBD, with a particular emphasis on investigational agents with novel mechanisms of action. Key data emerging from clinical trials were also presented.

Finally, Prof. Laurent Peyrin-Biroulet looked at the safety of IBD treatments and the importance of the mechanism of action. There was an introduction to the safety data available on investigational biological therapies. He discussed the impact of these treatments on infection and malignancy and explained the implications of systemic versus local immunosuppression.

These sessions were highly interactive, with electronic voting encouraging audience participation on a range of hot topics, such as: what has the greatest impact on your decision-making regarding choice of treatment for IBD; how to approach treatment in patients who lose response to biological agents; and what to consider to be the key considerations when comparing the safety of different agents.

Poster Synopsis

Orofacial Granulomatosis Associated with Perianal Disease Increases the Risk of Developing Intestinal Crohn's Disease

RM Goel,[1] E Hullah,[2] A Khan,[2] S Nayee,[2] N Shah,[2] H Campbell,[2] KV Patel,[1] M Escudier,[2] and JD Sanderson[1]

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Introduction

Orofacial Granulomatosis (OFG) is a rare chronic inflammatory condition of unknown aetiology, which is characterised by lip swelling, orofacial erythema and ulceration. A proportion of orofacial granulomatosis patients present with perianal disease in conjunction with their oral disease ('top and tail' disease). The cumulative risk of developing Crohn's disease (CD) in OFG patients is approximately 20% over a follow-up period of 20 years.[1] Perianal disease occurs in approximately one-third of CD patients and is associated with significant morbidity and a more severe disease course.[2] Perianal disease has been shown to occur in 12% of patients with ileal CD (L1), 41-92% of colonic CD (L2) and 15% of ileocolonic disease (L3).[3]

Aims and Methods

We retrospectively analysed a database of OFG patients. Patients with perianal disease were identified and compared to patients without perianal disease. The Montreal classification was used to classify the sites of patient's CD. We set out to determine how many of our OFG patients had concurrent perianal disease and how many of them went on to develop intestinal Crohn's Disease.

Results

263 patients with OFG were identified, of which 208 patients (79.09%) had OFG only and 55 patients (20.91%) had concurrent intestinal CD. Thirty-six patients (13.69%) had intestinal CD and no perianal disease. 19 patients ((7.22%) 13 male, median age 38 (IQR 25-49)) had intestinal CD and concurrent perianal disease.

Within the perianal group, all patients had concurrent intestinal CD. The commonest sites were colonic (L2) (8/19; 42.11%) and ileocolonic (L3)(8/19; 42.11%). The ileum (L1) was affected in 1 patient (1/19; 5.26%) and 2 patients had concomitant upper gastrointestinal CD with ileocolonic disease (L3+L4) (2/19; 10.53%).

The presence of OFG and perianal disease significantly increased the chances of developing intestinal CD (OR = 222, p = 0.0002, 2-tail Fisher Test).

In the perianal group, 11/19 patients (11/19; 57.89%) were diagnosed with CD prior to developing OFG. The median time to diagnosis of Orofacial Granulomatosis was 10 years after the diagnosis of intestinal Crohn's Disease.

Conclusions

Perianal disease in Crohn's disease is common and is associated with a more severe disease course.[2] Perianal disease in OFG patients is less common, however, and where it does occur it is always associated with intestinal CD in our cohort. The prevalence of perianal disease in OFG with concurrent CD is approximately one-third (the same as for OFG without CD). The ileum appears to be more commonly affected in OFG and perianal disease as compared with ileal involvement in CD and perianal disease. We suggest that patients with Orofacial Granulomatosis and perianal disease should be offered appropriate investigations such as ileocolonoscopy and/or small bowel MRI to investigate for intestinal CD.

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Rishi Goel graduated in 2004 from Guy's, King's and St Thomas' Medical Schools, London. After gaining comprehensive Medical experience working around London and Australia, he entered Gastroenterology and General Medicine specialist training in 2008 and is currently studying for an MD in orofacial granulomatosis and inflammatory bowel disease at Guy's and St Thomas' hospitals. He has published 12 peer-reviewed articles, authored many abstracts at international meetings and written 1 textbook chapter. He is due to be a sub-investigator in a new Crohn's disease treatment trial. His interests include therapeutic endoscopy, gastroscopy, colonoscopy, wireless capsule endoscopy, orofacial granulomatosis and inflammatory bowel disease.

Poster Synopsis

Accuracy of Invalid Fibroscans in Diagnosing Significant Liver Fibrosis

Bruno Moreira Gonçalves,[1] Ana Célia Caetano,[1, 2, 3] Dália Fernandes,[1] João-Bruno Soares,[1] Carla Rolanda,[1, 2, 3] Pedro Bastos,[1] and Raquel Gonçalves[1]

1. Department of Gastroenterology, Hospital de Braga; 2. Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Braga; 3. ICVS/3B's – PT Government Associate Laboratory, Braga/Guimarães

Introduction

Liver transient elastography (Fibroscan® - Echosens, Paris, France) is an instrumental method for non-invasive assessment of liver fibrosis. It is a simple, safe and efficient way estimate liver damage. The validity of FS results depends on three important parameters: (1) the need to get at least 10 valid measurements; (2) the interquartile range (IQR), which reflects the variability of the validated measures, and should not exceed 30% of the median value; (3) the success rate (the ratio of the number of successful measurements to the total number of acquisitions) should be at least 60%. It is essential to obtain these validity criteria in order to avoid an invalid procedure. The present study proposes to evaluate the diagnostic accuracy for significant liver fibrosis of the Fibroscans® (FS) considered invalid, by any of the three parameters.

Methods

The method undertaken was retrospective analysis of patients with invalid FS who underwent liver biopsy (LB) between 2008 and 2013 in our hospital. Significant fibrosis was defined as Metavir Fibrosis Score≥ 2. It determined the capacity (sensitivity, specificity, positive and negative predictive values and AUROC – Area Under Receiver Operating Characteristic) of invalid FS for the diagnosis of F ≥ 2, using the cut-off of liver stiffness for significant fibrosis according to the underlying pathology. Statistical analysis was performed with SPSS 20.0 for Mac®.

Results

From a total of 1123 FS, 78 were inconclusive, corresponding to a 6.9% rate of invalid exams. Of these, 56 underwent liver biopsy (Table 1). Most were male and the main indication for performing FS was staging chronic hepatitis B (37.5%). Most of the exams (51.8%) were invalid due to a success rate < 60%, with a median success rate of 43% (minimum 3% and maximum 46%). Thirty-two percent of the exams were inconclusive due to IQR/LS ratio > 30%, with a median ratio of 40.5% (minimum 34% and maximum 136.8%). LB revealed absence of significant fibrosis (F0 – F1) in 39 patients (69.6%). The sensitivity, specificity, positive and negative predictive values and AUROC for the diagnosis of F ≥ 2 was 76% (95% CI: 50-93%), 92% (95% CI: 79-98%), 81.2% (95% CI: 54.3 to 95.7%), 90% (95% CI: 76.3 to 97.1%), 0.84 (95% CI: 0.71 to 0.97, p <0:01).

Discussion and Conclusion

Transient elastography, using Fibroscan®, is a novel, non-invasive method that has been proposed for the assessment of liver fibrosis by measuring liver stiffness. Failure rates range between 2.4% and 9.4% in the different studies,[1] which are in agreement with our series (6.9%). When the FS is invalid, a liver biopsy should be considered to assess fibrosis and determinate the prognosis. To our knowledge there is no study addressing the accuracy of invalid FS for the diagnosis of significant fibrosis. Our study demonstrated a good capacity in these cases (AUROC 0.84), particularly in excluding significant fibrosis (specificity 92%, NPV 90%). The reason for invalid FS was not associated with significant change in the negative predictive value, which remained > 88%. In conclusion our study shows a good accuracy of na invalid FS in excluding significant liver fibrosis. These results needs further study and validation, and ultimately can change the need to meet all criteria of validity.

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Table 1. Characterisation of the patients		N=56 (%)
Number of patients:	Female	21 (37,5%)
	Male	35 (62,5%)
Mean age		47 ±11 years
Indication for Fibroscan®:	Chronic hepatitis B	21 (37,5%)
	Chronic hepatitis C	15 (26,8%)
	Non-alcoholic fatty liver disease	8 (14.3%)
	Other	12 (21.4%)
Reason for invalid Fibroscan®:	Sucess rate <60%	29 (51,8%)
	IQR/LS >30%	18 (32,1%)
	Both	9 (16,1%)
Degree of fibrosis on the liver biopsy:	F0	19
	F1	20
	F2	11
	F3	3
	F4	3

Table 2. Accuracy of invalid FS for the diagnosis of F ≥ 2 (95% CI)

Sensitivity	Specificity	PPV	NPV	AUROC
76%	92%	81,2%	90%	0.84
(50-93%)	(79-98%)	(54,3-95,7%)	(76,3-97,1%)	(0,71-0,97)

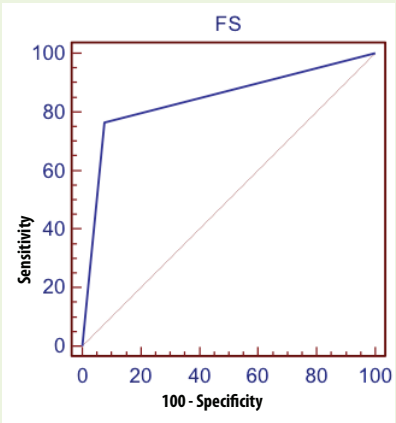

Figure 1. AUROC of invalid FS for the diagnosis of F≥2

Bruno Moreira Gonçalves finished his Medical degree in 2009, and since 2011 has been a resident of Gastroenterology in Hospital de Braga and at the University of Minho, both in Portugal. His research interests are the diagnosis and management of hepatic diseases. He is the author and co-author of several research works presented in national and international conferences.

Poster Synopsis

Functional Outcome of Patients Treated for Radiation-Induced Complete Esophageal Obstruction Following Successful Endoscopic Recanalisation

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Introduction

A rare side-effect of radiation therapy for head and neck cancer is the development of a complete esophageal obstruction. This means that this patient category is very small, and also difficult to treat. They are unable to have oral intake, which has a negative influence on the quality of life and there is a risk of aspiration.[1] In the past, an esophagectomy was the only treatment option to restore the swallowing function. Since the combined antegrade-retrograde dilation technique it is possible to recanalize the lumen of the esophagus endoscopically. This is safe and effective, especially in patients with a short stenosis.[2-6] In these few published small case series, subsequent removal of gastrostomy feeding tubes was feasible in approximately 50% of patients. The aim of this study was to assess the functional outcome of patients with a radiation-induced complete esophageal obstruction following successful endoscopic recanalisation.

Methods

A retrospective analysis was performed of all patients with radiation-induced complete esophageal obstruction who underwent successful endoscopic luminal recanalisation between August 2001 and February 2013 at a tertiary care centre. The only exclusion criteria was a follow-up of less than two weeks. Long-term functional outcome and factors predictive of clinical success were assessed. The definition of functional failure was when patients were unable to tolerate at least soft foods.

Results

A total of 35 patients were identified. Procedural-related adverse events occurred in four patients (11.2%), including three perforations which were managed conservatively. The mean number of dilations, including the recanalisation procedure, was 4.9. The mean maximal dilation diameter was 16mm. During a mean follow-up of 1.8 years, only 6 patients (19%) were dysphagia-free after the last treatment, although three of them required repeated dilations. Two patients had dysphagia to solids, three to semi-solids, six to liquids and 13 (42%) with complete dysphagia. Of 11 patients who had some ability to swallow, the feeding tube could be removed in 7, though 6 remained dilation-dependent. Only 4 (11%) patients were "treatment free" and 20 (57%) patients continued to require a gastrostomy feeding tube. Eleven (31%) patients died at the time of analysis, which could be related to the poor prognosis of head and neck cancer in general. One death was felt to be surgically-related and occurred within one month of a combined procedure involving otorhinolaryngology surgery. Head and neck cancer surgery was predictive of clinical success with 8/11 patients in the success group and 7/20 patients in the failure group ($p = 0.05$). A trend towards clinical success was seen when the time interval between radiation therapy and onset of dysphagia was longer (9.5 months vs. 1.2 months, $p = 0.07$).

Conclusion

The ability to swallow and maintain sufficient caloric intake orally after successful endoscopic recanalisation of radiation-induced complete esophageal obstruction is limited. A history of surgery for head and neck cancer is predictive for clinical success.

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Karina Grooteman graduated the Medical School of the University of Utrecht, The Netherlands in 2013. During medical school she was a research trainee at the Mayo Clinic, Rochester, Minnesota. The three research projects were focused on therapeutic endoscopy of the esophagus, including Zenker's diverticulum and the rule of three in esophageal dilation. She is looking to commence a PhD in the field of advanced endoscopy in the near future.

Poster Synopsis

Endoscopic Duodenal–Jejunal Bypass Liner New Treatment Option for Nonalcoholic Fatty Liver Disease?

Charlotte de Jonge, Sander Rensen, Ger Koek, Mandy Joosten, Wim Buurman, Nicole Bouvy, and Jan Willem Greve

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This work has been published as: de Jonge C, Rensen SS, Joosten MF, *et al*. Endoscopic duodenal-jejunal bypass liner rapidly improves plasma parameters of nonalcoholic Fatty liver disease. Clin Gastroenterol Hepatol. 2013 Nov;11(11):1517-20

Introduction

Recently, a non-surgical bariatric technique, the duodenal-jejunal bypass liner (DJBL, GI Dynamics, Lexington, MA), was developed (Figure 1). The initial purpose of the DJBL was to treat obesity. Remarkably, this device turned out to not only lead to significant weight loss, but also to rapid improvement of type 2 diabetes.[1] Since both conditions are important risk factors for NAFLD[2] and previous research with surgical bariatric techniques has revealed beneficial effects on NAFLD,[3] we hypothesised that DJBL treatment would also have a favourable impact on NAFLD.

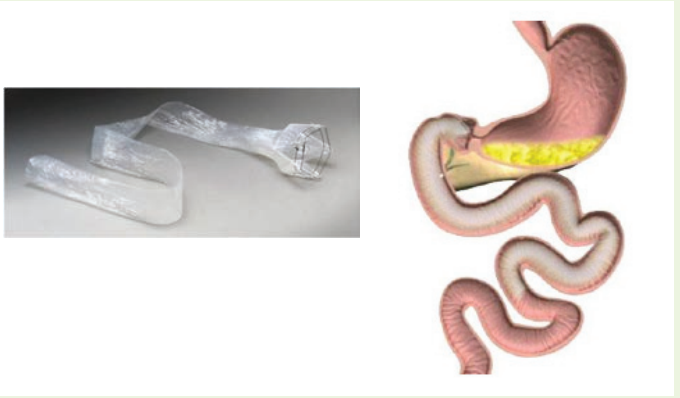

Figure 1. Diagram of a duodenal-jejunal bypass liner.

Methods

Seventeen subjects with obesity and type–2 diabetes were included in the Maastricht University Medical Center, Maastricht, and the Atrium Medical Center Parkstad, Heerlen, the Netherlands. They were treated with the DJBL for 24 weeks and studies on four occasions: within one month prior to the start of the study (D0), three and six months after implantation of the DJBL (M3 and M6 respectively), and again six months after explantation of the DJBL (M12). At these visits, body weight was determined and fasting venous blood samples were collected. Samples were immediately cooled, centrifuged and stored at -80 °C until further analysis of plasma levels of AST, ALT, γ-GT, caspase-cleaved CK-18 and L-FABP (liver fatty acid binding protein). Statistical analysis were performed using Wilcoxon signed rank test.

Results

DJBL treatment resulted in significant weight loss (Figure 2). In addition, the established clinical plasma liver parameters AST, ALT, and γ-GT decreased following DJBL implantation (Figure 3). Moreover, the levels of L-FABP and caspase-cleaved CK-18, plasma markers representing liver damage and liver apoptosis respectively, also decreased after initiation of DJBL treatment (Figure 4). Importantly, after explantation of the device, the levels of ALT, γ-GT, and caspase-cleaved CK-18 remained at a lower level (Figure 3, 4).

Discussion

We report for the first time that plasma liver parameters improve after duodenal-jejunal exclusion by DJBL. Our data show that clinical plasma liver parameters decreased following DJBL implantation. Normalisation of AST, ALT and γ-GT levels occurred in almost all subjects. Dixon *et al*. have shown that a decrease in γ-GT and AST levels is associated with improvement of liver histology in NAFLD patients following weight loss by bariatric surgery.[4] This advocates for improvement of NAFLD by DJBL treatment in our subjects. Additionally, DJBL treatment resulted in diminished levels plasma of L-FABP, a small intracellular protein that rapidly leaks out of damaged hepatocytes into the circulation.[5] A similar response pattern was observed for caspase-cleaved CK-18. Caspase-cleaved CK-18 is a protein generated during hepatocyte apoptosis, a prominent pathologic feature of NASH,[6] the more severe form of NAFLD. Plasma levels of caspase-cleaved CK-18 positively correlate with NAFLD severity, independently predicting the presence of NASH.[7] In our subjects, a decrease in caspase-cleaved CK-18 was observed after initiation of the DJBL treatment, potentially indicating NASH regression. Taken together, all plasma parameters associated with NAFLD improved after DJBL implantation.

Charlotte de Jonge was born in the Netherlands in 1985. Following medical school, she commenced her PhD, which focused on the effect of bariatric surgery on obesity and related diseases. This work has resulted in several publications, presentations, and prices. Currently, Charlotte is working as a surgical resident.

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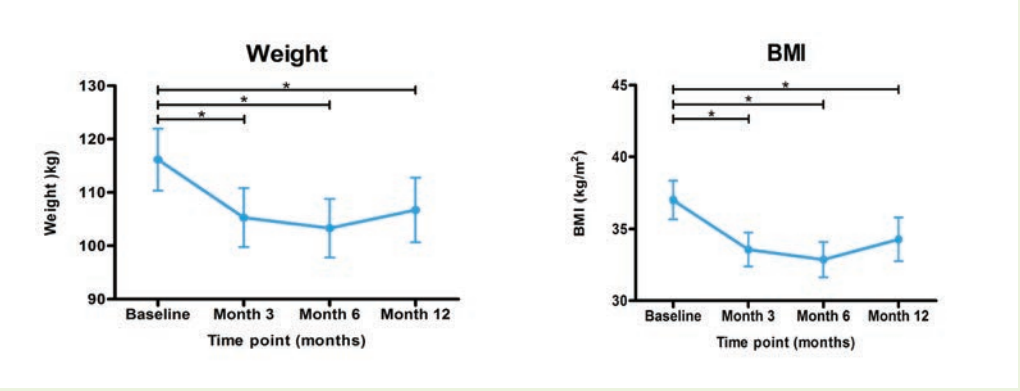

Figure 2. Duodenal-jejunal bypass liner treatment resulted in significant weight loss for participants.

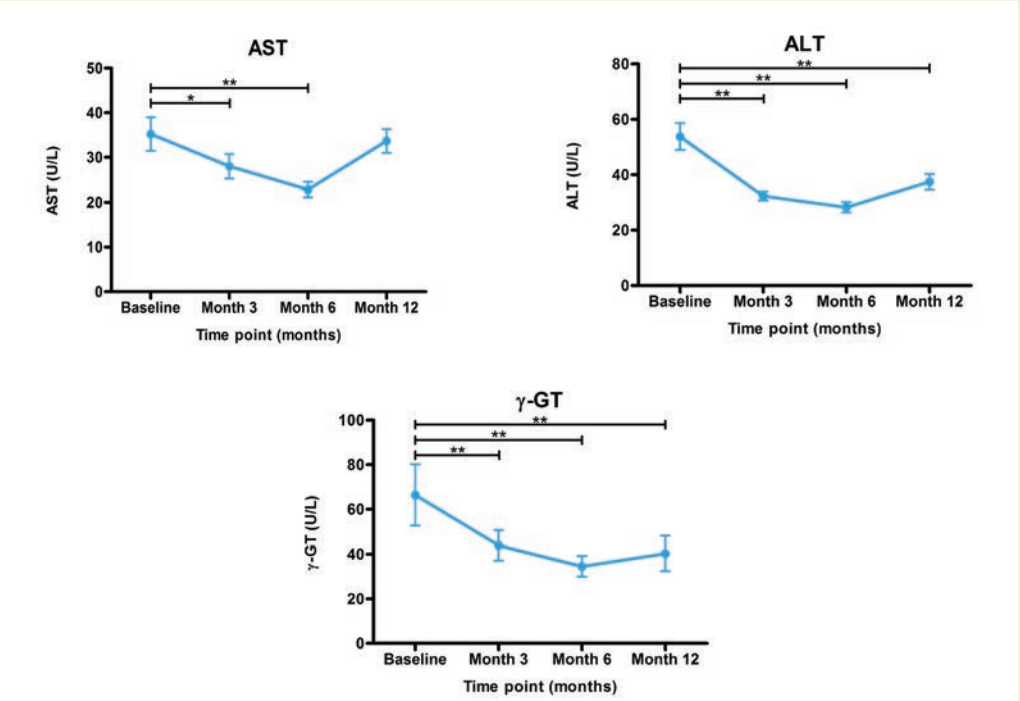

Figure 3. This figure shows that the established clinical plasma liver parameters AST, ALT, and γ-GT all decreased following DJBL implantation.

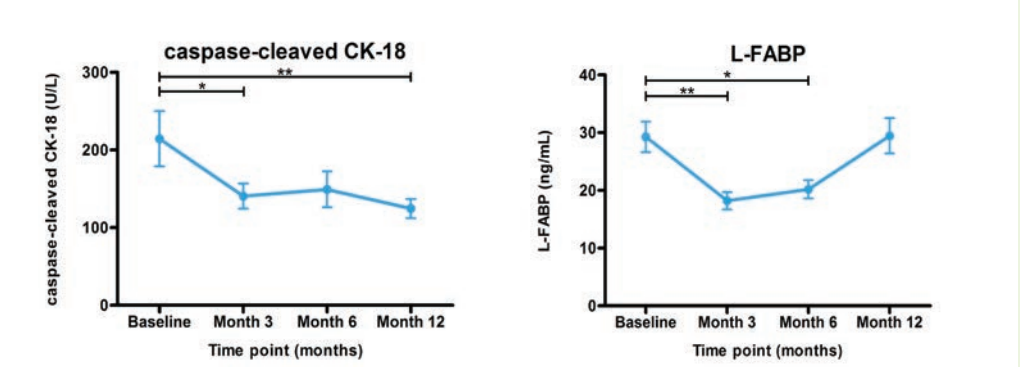

Figure 4. This figure shows that the levels of L-FABP and caspase-cleaved CK-18, plasma markers representing liver damage and liver apoptosis respectively, also decreased after initiation of DJBL treatment.

Poster Synopsis

Key Points and Techniques for Trans-nasal Endoscopic Screening for Superficial Hypopharyngeal Cancer

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With the progress made in endoscopy, there has been an increase in the number of superficial cancers in the head and neck region detected.[1] There are, however, some areas difficult to observe with trans-oral endoscopy. The circumferential observation of the hypopharyngeal mucosa is difficult during conventional endoscopy because of its anatomically closed nature, the pharyngeal reflex and salivary accumulation. Recently, we applied a new type of trans-nasal esophagogastroduodenoscope (EGD) [EG-580NW, Fuji Film, Tokyo, Japan] and modified endoscopic techniques to observe head and neck cancers, and obtained excellent results. The endoscope is a trans-nasal endoscope that can provide high quality endoscopic images to be viewed on a monitor and digitally recorded with a wide field view of 140 degrees.

Our screening was performed as follows. First, the patient is asked to bow their head deeply in the lateral position. We then put a hand on the back of the patient's head and push it forward. The patient is then asked to lift the chin as far as possible (lateral sniffing position). In order to inspect the oral cavity, we insert an endoscope without a mouthpiece and observe the upper, lateral and posterior wall of the oropharynx while the patient sticks their tongue forward. After observation of the buccal cavity, further oropharyngeal observation is carried out with a retroflexed endoscope inserted via the nose. When the tip of the endoscope reaching caudal to the uvula, the patient opens his mouth wide, sticks his tongue forward as much as possible and make a vocal sound like "ayyy". The endoscopist then makes the endoscope take a U-turn (the intra-oropharyngeal U-turn method) and observes the oropharynx, especially the radix linguae.

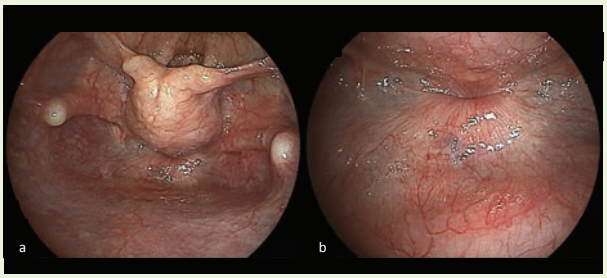

Figure1. a. The view of the hypopharynx obtained when using the modified Valsalva maneuver. b. The view of the orifice of the esophagus.

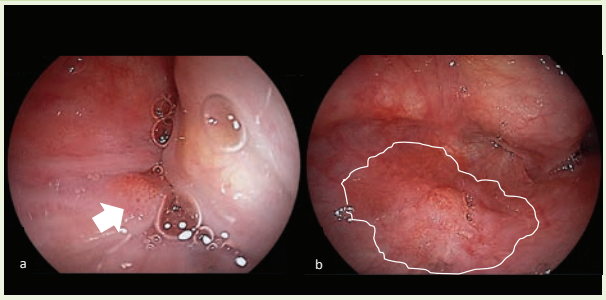

Figure 2. a. A slightly reddish area was observed at the posterior wall of the hypopharynx. The distal part of the tumor was unable to be observed. b. We could observe the whole lesion using the modified Valsalva maneuver.

To examine of the hypopharynx and the orifice of the esophagus, the patient is asked to blow hard and puff their cheeks while the mouth remains closed (The modified Valsalva maneuver[2]). The endoscopist pulls the patient's chin forward with the right hand. The position allows the posterior wall of the hypopharynx and the postcricoid subsite pharyngeal wall enables the pharyngeal mucosa and postcricoid region to be stretched out (Figure1a) and the orifice of the esophagus (Figure1b) to be visualised in an open space. The total time required to perform the procedure is approximately two minutes. It is easy to perform, and feasible for almost all patients.

Mucosal redness, a pale thickened mucosa, white deposits or loss of a normal vascular pattern are important characteristics that can be used to diagnose superficial carcinoma upon examination under white light. In addition, well demarcated areas covered with scattered dots observed upon closer observation of superficial microvascular structures and allows the detection of a lesion at an earlier stage. During a conventional screening, an endoscopic image of a hypopharyngeal cancer can be observed, but the distal part of the tumour cannot be observed (Figure 2a). An endoscopic image taken during modified Valsalva maneuver using trans-nasal ESD is shown in Figure 2b.The whole image of the tumour was able to be observed.

During the last four years, a total of 94 superficial head and neck cancers were found in 70 patients by trans-nasal EGD. A wide endoscopic view of the pharynx was obtained in a series of the procedures (Excellent in 87.9%, good in 4.5%, and poor in 7.6%). We successfully identified 13 small lesions, especially in the hypopharynx, that would not have been detected with the conventional method. This new method of screening for head and neck using trans-nasal endoscopy provided an excellent endoscopic field of view.

Kenro Kawada is an Assistant Professor at the Department of Esophageal and General Surgery at Tokyo Medical and Dental University. He is also a Specialist at the Japan Surgical Society, the Japan Bronchoesophagology Society and the Japan Society of Clinical Oncology. Dr. Kawada is also an expert at the Japan Gastrointestinal Endoscopy Society.

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Poster Synopsis

Use of Fabricated Allogeneic Epidermal Cell Sheets for Preventing the Esophageal Stricture After Circumferential ESD in a Porcine Model

Shinichiro Kobayashi,[1,2] Nobuo Kanai,[1] Masahiko Yamato,[1] Takahiro Hosoi,[1,3] Nobuyuki. Tanaka,[1] Teruo. Okano,[1] and Susumu Eguchi[2]

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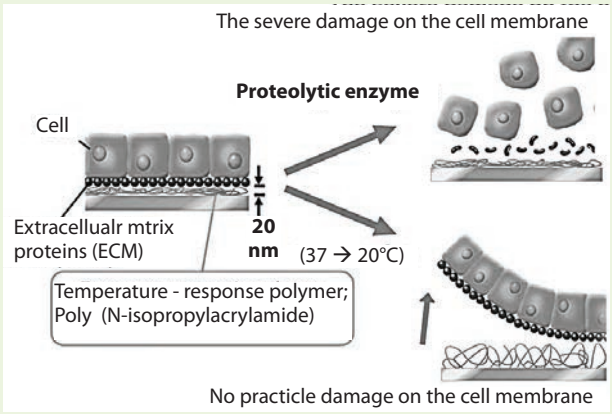
Okano and colleagues have developed a new strategy for cell culture methods and cell therapy with cell-sheets prepared on temperature-responsive polymer. Through this technology, various kinds of cell sheets can be harvested, not only without decrease in the number of cells but also with the preservation of superior cell-viability and cellular adhering ability.



Pre-clinical and clinical researches with cell sheets are in progress in various fields such as ophthalmology,[1] cardiology,[2] orthopedics,[3] periodontology,[4] and gastroenterology.[5, 6] To date, the clinical applications of cell sheets are limited, because cell sheets used in the clinical studies have been based on autologous transplantation, which requires patients' own tissue, the long cell sheet preparation period, and high-cost for the preparation.

Recently, several allogeneic living-cell based products have been developed and confirmed their efficacy on intractable skin ulcer and skin defect. Allogeneic cell based tissue engineering products also provide a new treatment strategy for gastroenterology, because allogeneic cells can give more quick, stable, and low-cost cell-based products than autologous ones.

Preparation and Characters of Fabricated Epidermal Cell Sheet

Epidermal cell sheets were fabricated from the cultured of isolated primary epidermal cells on the temperature-responsive membrane at 37 ºC for 2 weeks. After being incubated at 20 ºC for 20 min, epidermal cell sheets are non-invasively detached from the temperature-responsive membrane. The cell sheets were composed of basal and apical layers. Highly deposited extra-cellular matrix (ECM), which supports cell adhesiveness, was observed on the basal layer by a scanning electron microscope. Expressed keratin 1 of epidermal cell sheets was found to be similar to that of native epidermis by immunohistological analysis. Furthermore, expressed keratin 14 in the sheets was similar to that of esophageal mucosa. These results showed prepared epidermal cell sheets were able to be substituted for esophageal mucosa for covering artificial ulcer after esophageal endoscopic submucosal dissection (ESD).

Endoscopic Transplantation of Allogeneic Epidermal Cell Sheets for Preventing Esophageal Constrictions after ESD

The fabricated allogeneic epidermal cell sheets with support membranes were endoscopically transplanted immediately after ESD by using a forceps. In the preliminary experiment, esophageal constrictions and dysphagia of transplanted pigs after ESD were prevented, though pigs after esophageal ESD usually show severe esophageal constrictions for 2 or 3 weeks. In the transplanted group, enhanced mucosal healing and anti-inflammation were histologically observed at the ulcer site. However, the transplantation of epidermal cell sheets with forceps and support membranes was quite difficult. Prospective experiments will be required for establishing the stable transplantation of epidermal cell sheets. Furthermore, the additional research using selected and frozen allogeneic epidermal cells, having high-quality cells will be required for suitable clinical application.

Acknowledgments

The authors thank Takeshi Ohki, Makoto Kondo, Ichirei Takeda, and Yoshikazu Kumashiro who helped with this research and acknowledge the co-operation with the Department of Gastroenterology and Hepatology of Nagasaki University Graduate School of Biomedical Sciences, Endoscopy Division of National Cancer Center Hospital, and Endoscopy Division of National Cancer Center Hospital East.

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Shinichiro Kobayashi is a postgraduate student in Department of Surgery at Nagasaki University, Nagasaki, Japan. He is also a visiting scientist in Institute of Advanced Biomedical Engineering and Science at Tokyo Women's Medical University, Tokyo, Japan. He has been working on basic and clinical projects related to esophageal regeneration.

Poster Synopsis

Narrow Band Imaging-based Magnifying Endoscopy Potentially Predictive of Early Gastric Cancer in Borderline Lesions before ESD

Tadateru Maehata, Ryo Morita, Midori Suzuki, Satoko Nakatsu, Yoshinori Satoh, Yoshichika Oishi, Shinya Ishigooka, Kousuke Hosoya, Masahito Nomoto, Yoshiyuki Watanabe, Hiroshi Yasuda, and **Fumio Itoh**

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Introduction

Gastric cancer is the second leading cause of cancer deaths worldwide.[1] Endoscopic resection (ER) includes endoscopic submucosal dissection (ESD) is widely accepted as the standard treatment for early gastric cancer (EGC) without lymph node metastasis. The procedure has some advantages, in that it is minimally invasive, safe, and convenient.[2] Especially important is that large lesions can be resected *en bloc* by ESD technique. However, some incomplete resection will occur because we still do not have any appropriate diagnostic tool for decide benign-malignant borderline lesion. Recently, we have seen that narrowband imaging-based magnifying endoscopy (M-NBI) is more accurate than conventional white-light imaging (C-WLI) in the diagnosis of gastric cancer.[3, 4] Our goal is to clarify potentially useful findings to predict the existence of gastric cancer in borderline lesions diagnosed by M-NBI. In order to do so, we retrospectively analysed certain endoscopic features.

Methods

We diagnosed 168 consecutive gastric benign-malignant borderline lesions (152 cases) by C-WLI and M-NBI before ESD treatment. After we resected EGC lesions by ESD, we compared M-NBI diagnosis of borderline with pathological findings. GIF-H260Z (Olympus Corporation, Tokyo, Japan) was used for M-NBI. M-NBI diagnosis was classified according to VS (vessel plus surface) classification system. We classified the lesion's microvascular (MV) pattern as regular, irregular, or absent. Similarly, we classified the lesion's microsurface (MS) pattern as regular, irregular, or absent. We defined lesions as cancers according to the following criteria; the presence of irregular or absent MV pattern, the presence of irregular or absent MS pattern, or both. If the M-NBI findings did not meet these identified criteria, we classified the lesions as non-cancerous lesions.

Results

Macroscopic type and protruded type were found in 52 lesions. Flat and depressed type were found in 116. *En bloc* resection rate was in 167 out of 168 (99.4%). The final diagnosis for 149 lesions (88.7%) was adenocarcinoma (differentiated type were in 144, undifferentiated type were in 5), and for 19 lesions (11.3%) was adenoma. 168 lesions include 115 of mucosal and 34 of submucosal cancer. 156 out of 168 (92.8%) lesions could successfully diagnose of the tumour by M-NBI. There was no significant difference of diagnostic accuracy in tumour size: < 10mm, 36/42 (85.7%), >20mm, 54/62 (87.1%), < 20mm, 102/106 (96.2%). In other words, there was high diagnostic accuracy regardless of tumour size. However, we found 12 mismatch (M-NBI and pathological findings) lesions that were mostly slightly depressed type (9 lesions of slightly depressed type, 3 lesions of flat type). Moreover, we pathologically found intraluminal bridge form in one mismatch case. In other words, we were able to distinguish all protruded types of cancers.

Conclusion

We found that there was a high diagnostic accuracy by using M-NBI regardless of tumour size. We found 12 mismatch (M-NBI and pathological findings) lesions that were mostly slightly depressed type (9 lesions of slightly depressed type, 3 lesions of flat type). However, we were able to distinguish all protruded types of cancer. We also found that endoscopic findings using VS classification system were potentially predictive of EGC in borderline lesions diagnosed by M-NBI before ESD.

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Tadateru Maehata is a Gastroenterologist at St. Marianna University School of Medicine, Kawasaki, Japan, and specialises in the field of endoscopic treatment, such as Endoscopic submucosal dissection (ESD). He received his Ph.D. from St. Marianna University. Dr. Maehata's current research investigates minimally invasive treatment for gastrointestinal cancer.

Poster Synopsis

Identification of CD68+ Neutrophil Granulocytes in *In Vitro* Model of Acute Inflammation and Inflammatory Bowel Disease

Ahmad Amanzada, Ihtzaz Ahmed Malik, and **Federico Moriconi**

Division of Gastroenterology and Endocrinology, Department of Internal Medicine, University Medical Center, Georg-August-University Göttingen

Introduction

In contrast to the generally accepted concept of monocyte/macrophage specificity, many authors have reported some reactivity of anti-human CD-68 antibodies with antigens present on the cell surface of various haematopoietic and non-haematopoietic cells.[1] Recently published reports demonstrated both at the RNA and protein level that CD-68 was not only expressed in macrophages and monocytes, but was also expressed by non-myeloid cell types, such as T cells, fibroblasts, endothelial and tumour cells.[2,3] In acute tissue injury, the initial inflammatory cell influx consists predominantly of NGs (neutrophil granulocytes), which in turn orchestrate the recruitment of monocytes and the activation of lymphocytes required for a mature inflammatory response. Inflammatory bowel diseases, Crohn's disease (CD) and ulcerative colitis (UC), are characterised by an excessive recruitment of leukocytes from the blood circulation into the inflamed gut wall. During acute flares of UC or CD there is a massive infiltration of NGs into the affected mucosa, which is manifested clinically by an increase in stool NGs. IBDs are characterised by a dense infiltration of tissue by CD-68+ macrophages compared to non-inflamed colonic mucosa. This study investigated whether CD-68 positive NGs is found in peripheral blood and inflamed colonic mucosa if IBD patients.

Methods

PBMCs (peripheral blood mononuclear cells) and NGs were isolated from heparanised blood of healthy donors (n=3) and cultured as previously described.[4] Cells were stimulated *in vitro* with phytohaemagglutinin (5 µg/ml) or lipopolysaccharide (1 µg/ml) for 2, 4 and 8 hours. Cytospin preparation and immunofluorescent staining of PBMCs and NGs were performed as described previously. Double-immunofluorescence was performed according to an established protocol. Biopsy samples of the colon were obtained from six patients (3 men, 3 women) with CD, six patients with UC (4 men, 2 women) and three control subjects without detectable colonic disease (2 men, 1 women). The control biopsies were obtained from mucosa without any macroscopic evidence of inflammation in patients who underwent elective colonoscopic screening for cancer. The IBD patients had clinical and endoscopical signs of acute inflammation. IBD patients had clinical and endoscopic signs of acute inflammation. Protein extraction and Western blot analysis using PBMCs and NGs, but also THP-1, U-937, Hep-G2 and Jurkatt cells were performed as previously described. Gene and protein expression was analysed by real-time RT-PCR, Western blot and immunohistochemistry.

Results and Conclusion

Both PBMCs and NGs preparations contained cells that were positive for CD-68 and either neutrophil elastase (NE), or myeloperoxidase (MPO). CD-68+/NE-/MPO- cells were regarded as monocytes. CD-68 mRNA expression was detected in PBMCs and NGs preparations. With Western blot and by performing immunoprecipitation of cell lysate, we could clearly detect CD-68 in NGs, U-937, THP-1, Hep-G2, Jurkat cells and PBMCs. Identification of inflammatory cells in acutely inflamed colonic mucosa obtained from patients with IBD revealed a strong accumulation of CD-68+/MPO+ cells compared to normal colonic mucosa. The uptake of the marker by phagocytosis was excluded by performing a double staining with CD-163/NE and CD-163/MPO in PBMCs, NGs cultures and in inflamed colonic mucosa. The present findings need to be considered when immunohistological studies on cryostat or paraffin material from human inflammatory disorders are undertaken, as it is conceivable that a potentially erroneous impression of macrophage-derived damage is present.[5-7] The recognition of an increase in newly recruited CD-68+ cells at the site of tissue injury, together with the expression of both CD-68 and CD-11 b-c in pure granulocyte populations, opens a new window on the understanding of inflammatory responses and underscores the important role of these cells during the multistep process of tissue injury and repair. CD-68 is not only a marker for the macrophages-monocytes but also for NGs.

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Federico Moriconi graduated in Medicine at the University "La Sapienza" of Rome (2004). Since 2005 he has been working as a Medical Doctor and Researcher at the Clinic for Gastroenterology and Endocrinology of the University of Göttingen, Germany. Dr. Moriconi's research interest is the role of immune cells during cancer development.

Poster Synopsis

Laparoscopy-assisted Transgastric Endoscopic Retrograde Cholangiopancreatography (LA-ERCP) for the Management of Biliopancreatic Disorders in Bariatric Roux-en-Y Gastric Bypass (RYGB) Patients

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Introduction

Rapid weight loss after RYGB is a risk factor for the development of biliary complications, particularly cholelithiasis, with subsequent risk of choledocholithiasis and gallstone pancreatitis. Prophylactic cholecystectomy (CCE) at the time of RYGB may reduce future gallbladder-related morbidity however, to date, concomitant CCE is not recommended in obese patients undergoing RYGB since only a minority (about 7 to 8 percent in large studies) will become symptomatic and require delayed CCE.[1] Therefore, combined CCE would expose a lot of patients to an unnecessary procedure. In turn, endoscopic access to the biliary tree in post-RYGB patients with biliopancreatic disorders can be technically challenging due to specific anatomic rearrangements. In RYGB, a small pouch is created from the existing stomach and partitioned from the remainder of the stomach to exclude it completely from the passage of food. The small intestine is also divided into a biliopancreatic limb (duodenum and proximal jejunum) and a Roux limb (middle portion of the jejunum). The gastric pouch is connected to the proximal end of the Roux limb and the biliopancreatic limb is reconnected approximately 130 cm downstream on the Roux limb at the jejunojejunostomy.

Technical Considerations in Performing ERCP in RYGB Patients

To perform ERCP in RYGB patients, access to the pancreaticobiliary limb is necessary. The long anatomic route prevents passage to the major papilla with a conventional side-viewing duodenoscope. One option is to perform an enteroscopy-assisted ERCP (EA-ERCP) which is in fact a retrograde endoscopy with a long endoscope (colonoscopes or enteroscopes), passed via the gastric pouch and the Roux limb and then up the biliopancreatic limb to the major papilla. Disadvantages are the long procedural time and the difficult orientation of endoscopic equipment. The papilla is usually reached from a different angle as with a duodenoscope, which leads to a different and more difficult approach for biliary cannulation. Enteroscopes also usually lack an elevator so scope positioning has to be precise in order to manoeuvre the endoscopic instruments in the correct orientation. Another disadvantage of EA-ERCP is the limited availability of instruments required for performing ERCP. The estimated success rate (i.e. biliary cannulation) is approximately 60% in most of the literature.

Another option is to perform ERCP through a minimally invasive access to the stomach with a laparoscopy-assisted gastrostomy. After standard laparoscopic access to the abdominal cavity is accomplished, a gastrotomy is performed with ultrasonic shears and a purse-string suture is placed around it for traction. Subsequently, a side-viewing endoscope is introduced through a 15 mm trocar placed into the gastrotomy and ERCP is completed under fluoroscopic guidance. LA-ERCP has shown to be superior to EA-ERCP in terms of therapeutic success rate (biliary cannulation rates up to 100% have been described) and is associated with shorter procedure times.[2]

LA-ERCP: "The Belgian Experience"

We recently reviewed the data of 20 post-RYGB patients who underwent a laparoscopy-assisted ERCP in four Belgian centres in the period May 2008 to April 2013. Indications mainly included ascending cholangitis, choledocholithiasis and recurrent biliary pancreatitis. 14 patients underwent concomitant CCE, 6 patients already had history of prior CCE. All patients underwent successful biliary cannulation and sphincterotomy (+ stone extraction). The mean endoscopic procedure time was 53.4 minutes (range 15-120). No ERCP-related complications (i.e. bleeding, pancreatitis or retroperitoneal perforation) occurred. Mean hospital stay was 3.3 days (range 2-5).

Conclusions

Despite the relatively small number of patients, our study clearly showed that LA-ERCP is a feasible approach in the treatment of biliopancreatic disorders in post-RYGB patients, with short procedure times and without major complications in our series. This technique also allows for ERCP and CCE to be performed consecutively in a single procedure. In post-RYGB patients without prior CCE and with complicated gallstone disease (e.g. choledocholithiasis, ascending cholangitis, …), combining cholecystectomy and LA-ERCP could be a valid approach.

Christophe Snauwaert is a Gastroenterologist at Department of Hepatology and Gastroenterology at the Ghent University Hospital in Ghent, Belgium. He received his medical degree in 2007 and finished his training in 2013. Dr. Snauwaert is particularly interested in diagnostic and therapeutic endoscopy and is currently completing an additional year of his fellowship dedicated to advanced endoscopic procedures such as ERCP.

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Poster Synopsis

Diagnosis and Quantitative Assesment of Duodenogastric Reflux in Patients after Cholecystectomy

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Introduction

Symptoms of duodenogastric reflux as heartburn, eructation, feeling of bitterness in the mouth and etc. are often observed in patients after cholecystectomy. X-ray andendoscopic examinations are used for the diagnosis of this condition. However, quantitative characteristics of these methods is rather subjective.

Aims and Methods

The aim of the research was to give a quantitative assessment of the duodenogastric reflux (DGR) in patients after cholecystectomy. 98 patients (11 men and 87 women, aged 24-82 years) after cholecystectomy were x-rayed, underwent endoscopic examination of upper gastrointestinal tract and hepatobiliary scintigraphy. To estimate the bile passage a radionuclide tracer 99 mTc HIDA was used, with fatty meal ingestion after 45 minutes. The degree of DGR was defined by a percentage ratio of total radioactivity in a gastric area to radioactivity in the duodenal area which exceeded 15% of the background radiation. (Figure 1). DGR was distributed to 4 degrees: I - from 16 to 35%; II - 36-55%; III - 56-75%; IV - more than 75%.

Results

DGR was revealed in 47 (47.9%) post-cholecystectomy patients. The 1st degree was revealed in 22 (46.8%), 2nd - in 7 (14.9%), 3rd - in 13 (27.7%), 4th - in 5 (10.6%) patients. Patients with DGR more often demonstrated x-ray signs of duodenal antiperistalsis ($p<0.001$) and incompetence of the cardia ($p=0.02$) than those who did not have isotope reflux to the stomach. Intensity of DGR correlated with radiological data of the duodenal antiperistalsis ($Rs=0.45$; $p<0.05$) and regurgitation of contrast substance from the duodenum to the stomach ($Rs=0.54$; $p<0.05$) (Figure 2).

The stage of DGR had an association with endoscopic signs of pyloric sphincter function decrease ($Rs=0.45$; $p<0.05$). Moreover, the patients with the 3rd and 4th degrees of DGR had gastroesophageal reflux disease manifestations. Gastroesophageal reflux, determined by x-ray examination, was confirmed during endoscopy by reflux esophagitis manifestation (Figure 3).

Pyloric incompetence ($p<0.001$) and a bile reflux ($p<0.001$) of the patients with DGR were more often revealed during endoscopy procedure. Sensitivity of the scintigraphic diagnostic procedures of DGR made up 81%, specificity – 72%.

Conclusion

Hepatobiliary scintigraphy may be accepted as an informative diagnostic method and quantitative assessment of DGR in patients after cholecystectomy. On an increase of bile regurgitation to the stomach the reflux extends and reaches t he gullet, forming "a double reflux".

The findings of this method can be used in anti-reflux treatment selection.

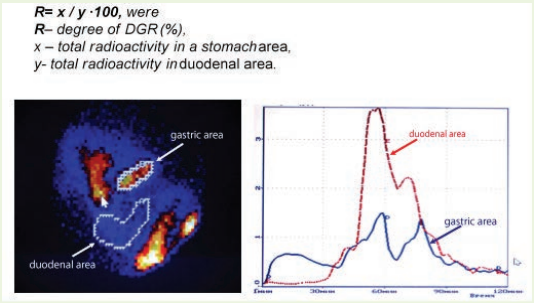

Figure 1. Quantitative hepatobiliary scintigraphy: definition of degree of DGR -the duodenogastric bile reflux (red line).

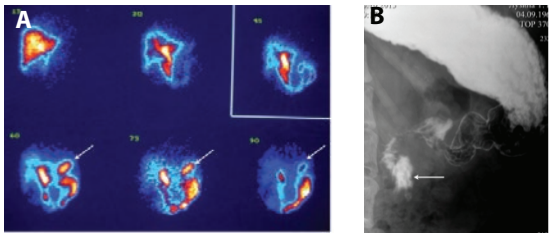

Figure 2. a) Quantitative hepatobiliary scintigraphy: on the 45, 60, 75 and 90 minutes duodenogastric bile reflux is observed (arrows); b) X-ray examination- duodenal antiperistalsis and regurgitation of contrast substance.

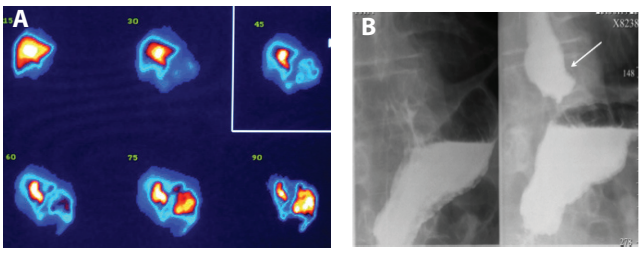

Figure 3. Quantitative hepatobiliary scintigraphy: on the 60 and 75th minute the duodenogastric bile reflux is observed; b) X-ray examination gastroesophageal reflux.

Dr. Repin is a Professor of the Chair of Surgery of the Postgraduate Education of Perm State Academy of Medicine. He graduated from Perm State Institution of Medicin in 1982, and in 2005 he completed a thesis entitled "Surgical correction and prevention of the postoperative disturbances of gastric and duodenal motor -evacuator function".

Poster Synopsis

In Vivo Observation of the Esophagus by Intraluminal and Transmural Endoscopy: Anatomical Lessons from Advanced Endoscopy

Roberta Maselli,[1,2] Haruhiro Inoue,[1] Haruo Ikeda,[1] Manabu Onimaru,[1] Akira Yoshida,[1] Esperanza Grace Santi,[1] Hiroki Sato MD,[1] Makoto Kaga,[1] Bu'Hussain Hayee[1,2,3] and Shin-ei Kudo[1]

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Introduction

Since the introduction of the flexible endoscope in 1950s, physicians have been able to explore the gastrointestinal tract, but especially in the past 10 years endoscopic diagnostics has benefited from technologies such magnification (M) and narrow band imaging (NBI). This study summarises the esophageal wall anatomy by intraluminal and transluminal endoscopy.

Material and Methods

From May 2008 to August 2012, 39459 diagnostic and 519 therapeutic upper GI endoscopies (242 EMR/ESD, 265 POEM, 12 SET) were performed. For each endoscopy digital images were collected and analysed by experienced endoscopists.

Results

Normal appearance of the esophageal vasculature IPCLs are terminal vessels in the epithelial papilla, demonstrated most clearly with M-NBI, but visible even without this modality (i.e. with magnification alone). Characteristic changes in these vessels correspond to the depth of invasion of esophageal cancer, facilitating early treatment decisions. Blood flow from IPCLs collects to branching vessels located within the lamina propria. The entire esophageal wall was organised in the following way (from the lumen to outside) (Figure 1):

- Mucosa. IPCLs and the meshed sub-epithelial capillary network (SECN) can be visualised along the entire esophagus. These drain into branching vessels and finally to the submucosal drainage vessels.
- Submucosa: This is a virtual space, connecting the mucosa to the muscle layer. The drainage vessels are found along the entire length of the esophagus; they become elongated at the esophagogastric junction (GEJ).
- The muscle layer is composed of inner circular and outer longitudinal fibres. A venous network exists within the intramuscular space. Perforating vessels are observed here; they connect the submucosal drainage veins/arteries with the main longitudinal vessels outside the adventitia.
- The adventitia is a very thin layer, covering the external esophageal side. After myotomy during submucosal endoscopy, the peri-esophageal venous network is revealed in this layer.

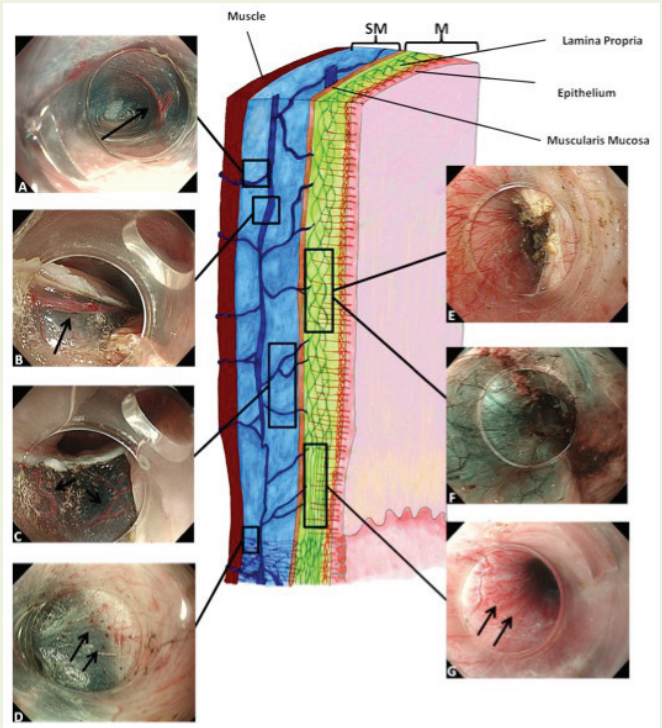

Figure 1. Schematic illustration the esophageal wall and the esophago-gastric junction with the endoscopic corresponding images. Vessels are indicated with black arrows. A. Perforating vessel from the outer esophagus to the submucosal vessel, passing through the muscle layer; image captured during POEM (bottom side muscle layer, left side submucosal lifting) B. Submucosal drainage vessel during ESD; C. Submucosal vessels connecting the drainage veins with the mucosal (lamina propria) branching vessels; D. Spindle veins immediately below the GEJ (in left side of the image in blue the submucosa and in the right side the muscle); E and F. White light and NBI of the Branching vessels. The view is from inside the submucosal tunnel (backside of the mucosa on the left, muscle –already cut- on the right). G. Passage of GEJ. See, in different planes, all the vessel of the submucosa and lamina propria (palisade vessels).

GEJ Landmarks at the GEJ

From the mucosal side, the GEJ can be defined as region in which the distal ends of esophageal longitudinal vessels (palisade vessels) meet the proximal ends of gastric mucosal folds. Advanced Therapeutic Endoscopic procedure, involving entry into the submucosa, allows these structures to be seen directly. Branching vessels are contiguous with palisade vessels as they run in the same plane just above the muscularis mucosae.

Just distal to the GEJ, small veins, which we termed 'spindle veins', are present in the submucosal layer, running closely and parallel to each other, perpendicular to the muscle layer. These are found in more than 70% of patients undergoing submucosal endoscopy and act as a reliable landmark that the GEJ has been passed.

Discussion

Endoscopic evaluation of the esophageal vasculature is now possible *in vivo* with advanced endoscopic technology and techniques. Our descriptions of anatomical landmarks, will serve to inform the practice of endoscopic diagnosis and surgery in the future.

Roberta Maselli graduated in medicine at the "Sapienza" University of Rome, in 2006. She is trained in both gastroenterology and gastrointestinal surgery and is currently a Doctoral student studying the endoscopic diagnosis and treatment of early GI neoplasias. Dr. Maselli was trained in Japan for 1 year and in India for 6 months.

Poster Synopsis

Use of Ancillary Techniques In Improving The Yield of Samples Obtained at EUS-FNA of Thoracic and Abdominal Lymph Nodes

M. A. Yusuf A. Loya, and M. Nadeem

Shaukat Khanum Memorial Cancer Hospital & Research Centre, Lahore

Introduction

Thoracic and abdominal lymph nodes may be enlarged in a number of neoplastic and non-neoplastic disorders. Because of their location, obtaining tissue from thoraco-abdominal lymph nodes has been difficult and has usually involved some form of image-guidance. Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) allows tissue acquisition from these locations, is less invasive, more cost-effective and has lower complication rates.

Ancillary techniques such as special histochemistry (SHC) and immunohistochemistry (IHC) are increasingly used in reaching a definitive diagnosis in histopathology and cytopathology.[1-4] When examining tissue from thoracic and abdominal lymph nodes, the importance of these ancillary techniques is heightened, because the quantity of material obtained is often small. Hence, every effort should be made to utilise the tissue in an optimal manner, so as to reach a conclusive diagnosis. With the use of SHC, IHC and other ancillary techniques on cytological material, the diagnostic yield can be increased significantly.[5]

We evaluated the use of SHC, IHC and other ancillary techniques such as flow cytometry on cytological material obtained by EUS-FNA from thoracic and abdominal lymph nodes, to show how these techniques can improve the diagnostic yield.

Material and Methods

We gathered data retrospectively on 287 patients (age range 8-87y) who underwent EUS-FNA from enlarged thoracic and abdominal nodes between November 2005 and December 2012. An on-site cytopathologist determined the adequacy of cytology material during the EUS-FNA procedure and additional passes were made when necessary in order to obtain material for cellblock preparation. We compared the preliminary diagnosis made after routine cytological stains (i.e. DiffQuik & Papanicolaou stain) with the final diagnosis made after performing SHC, IHC & flow cytometric studies.

Results

Ancillary studies were performed in 111/287 EUS-FNA procedures on thoracic and abdominal lymph nodes. Of these, 27 were neoplastic cases. IHC stains were performed in 24 out of 27 neoplastic cases. In the remaining three neoplastic cases, flow cytometry was performed. SHC staining was performed in all 84 non-neoplastic cases.

The most commonly employed IHC marker was the CD30 antibody, which was used in 9 cases (37.5%), followed by cytokeratin (AE1/AE3) in 5 (20.8%). Other markers used were CD3, CD15, AMACR, CD56, CD117, HepPar-1, P63, TTF1, EMA and PSA.

IHC stains were found to be contributory in 19/24 (79.16%) cases. In 16 (66.6%) cases it provided a major clue to the diagnosis while in 3 (12.5%) cases, it helped further characterise the lesion. The most frequent diagnosis made was metastatic carcinoma, followed by classic Hodgkin's lymphoma (CHL) in 6 (25%) cases. Other diagnoses were diffuse large B cell non-Hodgkin's lymphoma (DLBCL), metastatic gastrointestinal stromal tumor (GIST) and metastatic neuroendocrine tumour (NET). In 5 (20.8%) cases IHC stains were found to be non-contributory.

Flow cytometry led to a definitive diagnosis in 3/3 neoplastic cases – DLBCL in two and chronic lymphocytic leukemia (CLL) in the third. SHC stains were performed in 85 cases, of which one was in a patient with a neoplastic condition, in association with IHC markers, while the other 84 cases were non-neoplastic. After routine cytological staining, granulomata were diagnosed in 72 cases (85.7%), while 7 (8.3%) cases showed lymphoid tissue with necrotic and calcified material. Lastly in 5 (5.9%) cases, reactive lymphoid hyperplasia was seen.

In all 84 non-neoplastic cases, ZN stain was the only stain performed for acid-fast bacilli (AFB). In 4 cases, other additional stains were also performed, including PAS stain in two and mucicarmine and GMS stains in one each.

In 80 non-neoplastic cases FNA material was also submitted for tuberculosis culture, and was positive in 8 patients. In 84 non-neoplastic cases, SHC stains were found to be useful in 3 cases (3.57%). ZN stains revealed AFB in 2 cases (2.38%), while in 1 (1.19%) case, PAS stain revealed fungal hyphae compatible with Aspergillus infection. In the remaining 81 (96.42%) non-neoplastic cases, SHC stains did not add to the initial diagnosis made after routine cytological staining.

Conclusion

As EUS-FNA becomes more widely available, it is important that clinicians and pathologists be aware that the use of ancillary studies in EUS-FNA of thoracic and abdominal lymph node is an effective tool in improving and enhancing the cytologic diagnoses obtained by this very useful endoscopic technique.

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Muhammed Aasim Yusuf is a Gastroenterologist with a particular interest and expertise in therapeutic endoscopy in gastrointestinal cancer. He graduated from the King Edward Medical College, Lahore in 1986 and trained in Canterbury, and Birmingham, UK. He received his Membership of the Royal Colleges of Physicians of the UK in 1991, and was elected as a Fellow in 2000.

Microscopic Colitis – New Insights in an Emerging Disease

Introduction

The evening symposium entitled, "Microscopic Colitis – New Insights in an Emerging Disease" was held during UEG Week 2013 on Tuesday 15th October 2013 in Berlin, Germany. The symposium was chaired by Prof. Dr. Stephan Miehlke, Gastrointestinal Centre Medical Centre, Eppendorf, Hamburg, Germany and Prof. Dr. Curt Tysk, Örebro University Hospital, Örebro, Sweden. The Falk Evening symposium was organised in collaboration with the European Microscopic Colitis Group.

Microscopic Colitis – New Insights in an Emerging Disease
Dr. Falk Pharma Sponsored Evening Symposium at the United European Gastroenterology (UEG) Week 2013, Berlin, Germany, 15th October 2013

Chairs: Prof. Dr. Stephan Miehlke, Gastrointestinal Centre Medical Centre, Eppendorf, Hamburg, Germany

Prof. Dr. Curt Tysk, Örebro University Hospital, Örebro, Sweden

Welcome and Introduction
Prof. Dr. Stephan Miehlke, Gastrointestinal Centre Medical Centre, Eppendorf, Hamburg, Germany and Prof. Dr. Curt Tysk, Örebro University Hospital, Örebro, Sweden

What Do We Learn From Epidemiological Studies?
Dr. Ole K. Bonderup, Silkeborg Hospital, Silkeborg, Denmark

Histopathological Spectrum – How Reliable is the Pathologist?
PD Dr. Daniela Aust, University Hospital Dresden, Dresden, Germany

Pathophysiology – What is Certain and What Needs to be Explored?
Dr. Marieke J. Pierik, Academic Hospital Maastricht, Maastricht, The Netherlands

Burden of Disease – It is not Just Diarrhoea!
Dr. Andreas Münch, University Hospital of Linköping, Linköping, Sweden

Evidence-based Therapy and Unsolved Problems
Prof. Dr. Stephan Miehlke, Gastrointestinal Centre Medical Centre, Eppendorf, Hamburg, Germany

Closing Remarks
Prof. Dr. Curt Tysk, Örebro University Hospital, Örebro, Sweden

Background

Microscopic colitis is a disease that is attracting increasing attention. Long underestimated, it is now increasingly clear that it is a chronic inflammatory bowel disease, such as ulcerative colitis and Crohn's disease. Microscopic colitis was also recently recognised as a disease in its own right by the European Crohn's and Colitis Organisation (ECCO) in its current guidelines. Within this symposium, international experts discussed current knowledge of the disease, which has now been found to encompass a third form – incomplete colitis – in addition to collagenous and lymphocytic colitis.

Chronic watery non-bloody diarrhoea is the main symptom of microscopic colitis, a disease that remained unrecognised as such for a long time. Crucially, there are no clear pathophysiological endoscopic abnormalities, in contrast with Crohn's disease and ulcerative colitis. Diagnosis of the disease rests entirely on characteristic histological findings, which are an increased number of lymphocytes (>20 IEL/100 epithelia, Figure 1) in the lamina propria of the colonic mucosa for lymphocytic colitis, while collagenous colitis there displays a thickened subepithelial collagen band (> 10 µm, Figure 2).

"However, there is now no longer any doubt that microscopic colitis is a chronic inflammatory bowel disease. The disease is also associated with a significant reduction in patients' quality of life," Prof. Dr. Stephan Miehlke, Hamburg (Germany), emphasised. So far, the only approved and evidence-based treatment option for microscopic colitis is budesonide, a topical glucocorticoid with high local activity but low systemic availability.

Increasingly Frequent Diagnosis

Microscopic colitis was first described in 1976 and is diagnosed more and more frequently. According to Dr. Ole K. Bonderup, Silkeborg (Denmark), this is evidence of rising incidence. The incidence of both collagenous colitis and lymphocytic colitis has risen steadily since the early 1980s. However, it should also be borne in mind that this period has also seen a parallel rise in the use of biopsies and histological investigations. "The apparent rise in incidence may therefore also be a function of the increasingly frequent use of biopsies", Dr. Bonderup explained. Although collagenous and lymphocytic colitis were previously assumed to be rare cases, there i now clear evidence that this is not the case.

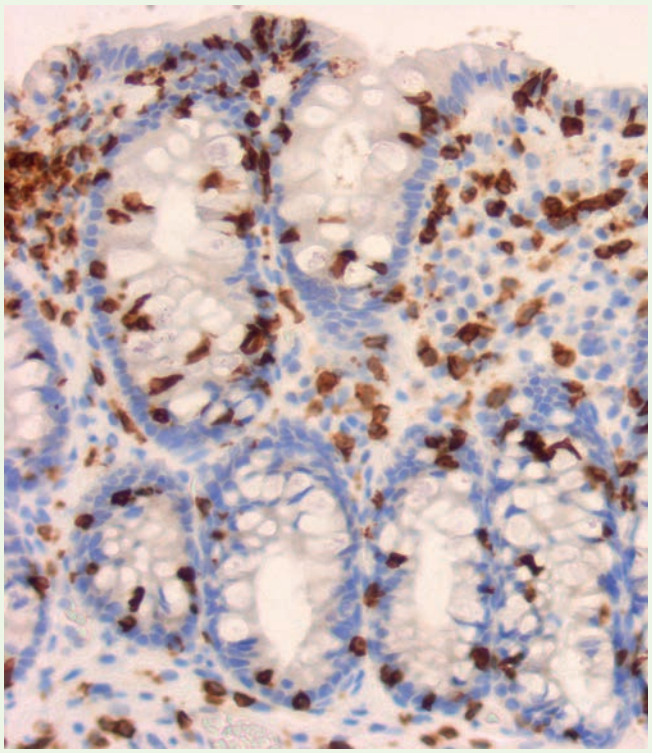


Figure 1. Immunohistological representation of intraepithelial lymphocytes (CD3, 20x) in lymphocytic colitis.

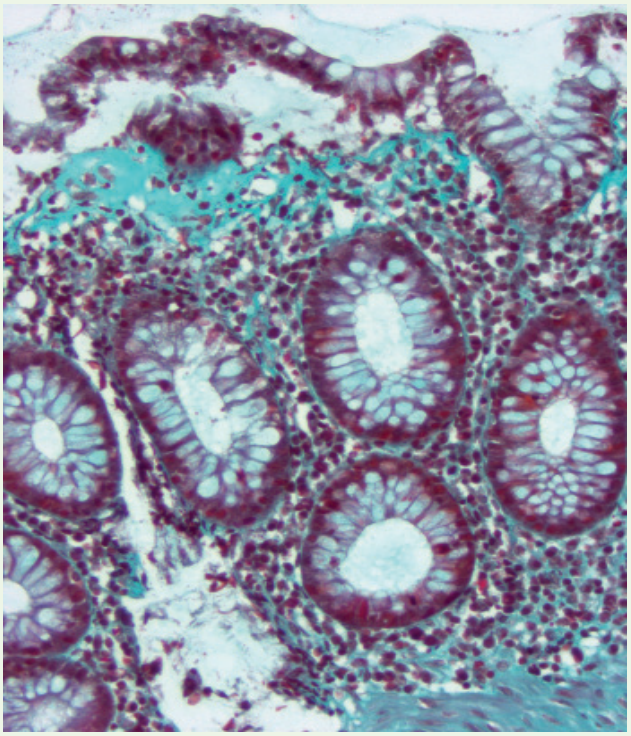


Figure 2. Collagenous colitis with thickened subepithelial collagen band and detached regressively changed surface epithelium (Goldner stain, 20x).

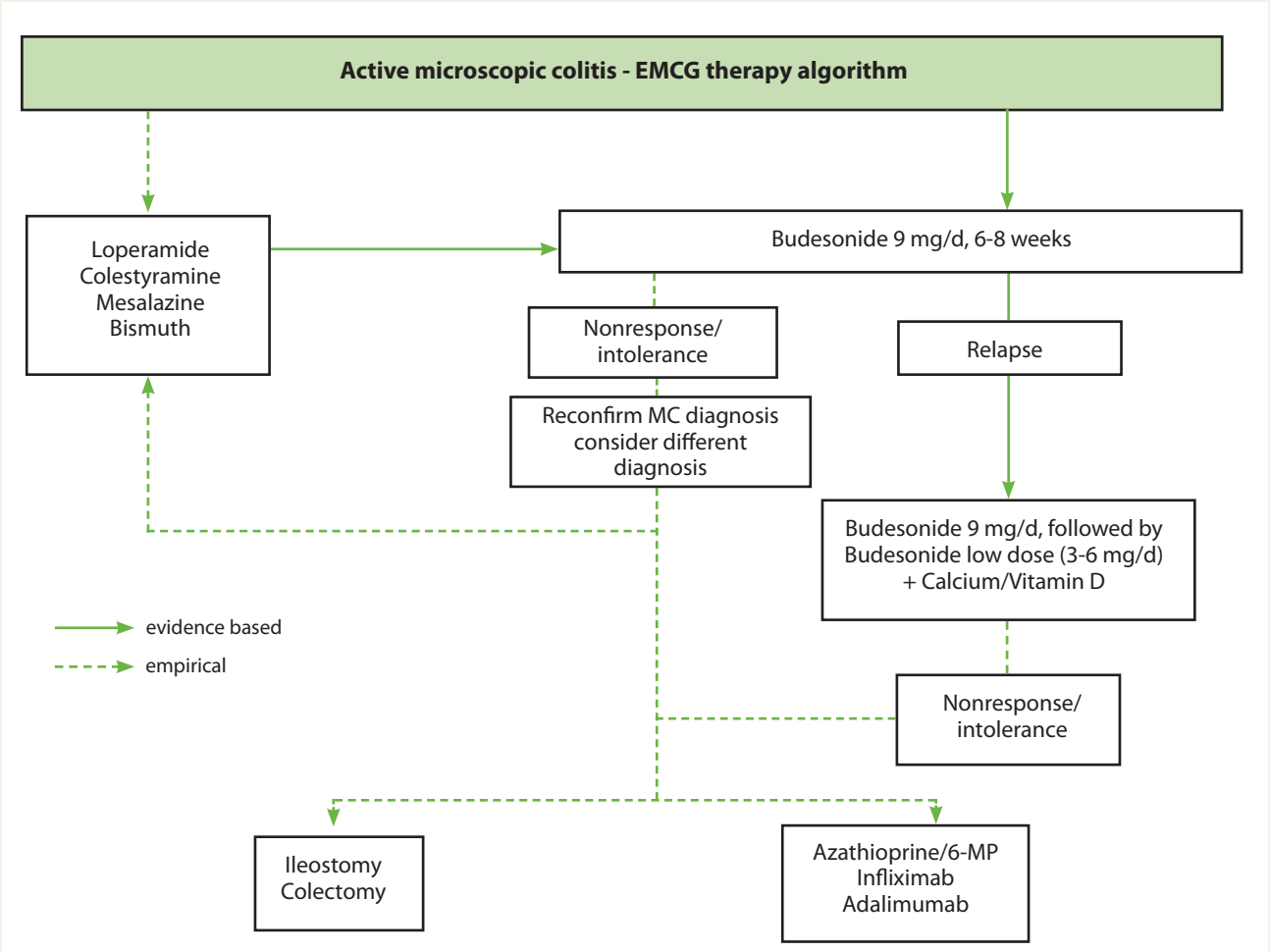


Figure 2. Microscopic colitis – EMCG therapy algorithm (2012).

Differential Diagnosis irritable bowel syndrome - microscopic colitis		
	Irritable bowel syndrome	**Microscopic colitis**
First occurance of disease	Commonly younger than 50 years of age	Commonly older than 50 years of age
Stool consistency	Soft - variable - hard	Watery/soft
Abdominal pain/ discomfort	Obligatory	Variable
Nocturnal diarrhoea	Very Rare	Possible
Feeling of incomplete bowel evacuation	Common	No
Weight loss	Rare	Common
Faecal incontinence	Rare	Common
Feeling of fullness/ bloating	Common	Rare
Accompanying autoimmune disease	No	Yes
Influenced by stress	Possible	Possible
Accompanying psychosomatic disease	Common	Rare
Suspected drug induced diarrhoea	No	Yes

Figure 4. Differential diagnosis irritable bowel syndrome – microscopic colitis.

Differential Diagnosis of Irritable Bowel Syndrome

In fact, the estimated incidence of microscopic colitis is 10–12/100,000 and, according to Dr. Bonderup, it is reasonable to assume that a high number of cases go undetected. The disease has a worldwide distribution. However, incidence rates vary by country, although this might be caused by inaccurate diagnoses. Therefore, we can assume that the disease goes undetected or is misdiagnosed in many patients. Dr. Bonderup cited irritable bowel syndrome (Figure 4) and other chronic inflammatory bowel diseases such as ulcerative colitis and Crohn's disease as the most significant differential diagnoses.

Risk Factors for Microscopic Colitis

"There is a striking female predominance in microscopic colitis," Dr. Bonderup reported. However, reported figures for this parameter again vary by country. In Sweden, a female:male ratio of 4.3:1 is currently reported for collagenous colitis, whereas in Iceland the proportion of women is significantly higher at 7.9:1. There are also clear risk factors such as smoking. Age also appears to be a risk factor to some extent since the likelihood of contracting the disease increases with age. There is also an association with the use of proton pump inhibitors (PPI) and non-steroidal anti-inflammatory drugs (NSAIDs). To a lesser extent, there is also an association with treatments using statins and (for lymphocytic colitis) with selective serotonin reuptake inhibitors (SSRIs) (Figure 5).

Diagnosis Based on Histology

Diagnosis of microscopic colitis, according to PD Dr. Daniela Aust, Dresden (Germany), is by histology. The characteristic feature of lymphocytic colitis is an increased proportion of surface intraepithelial lymphocytes (IEL), defined as more than 20 IELs per 100 epithelial cells. The lamina propria usually shows increased numbers of plasma cells and lymphocytes with normal crypt architecture (Figure 1). Where the number of IELs is between 10 and 20/100 epithelial cells, the patient may have incomplete colitis, according to Dr. Aust. This form of the disease also typically involves a slight thickening of the subepithelial collagen band, although this is much less pronounced than in cases of collagenous colitis. Diagnosis of this form of the disease relies on the histological evidence of a subepithelial collagen band with a depth of more than 10 µm. In collagenous colitis, the IEL count is only slightly increased, usually between 10 and 20 cells per 100 epithelial cells (Figure 2).

Pathogenesis Still Largely Unknown

Diagnosis of microscopic colitis can be anticipated in around 13% of patients with chronic diarrhoea, Dr. Marieke J. Pierik, Maastricht (The Netherlands) explained. The disease develops on the basis of genetic

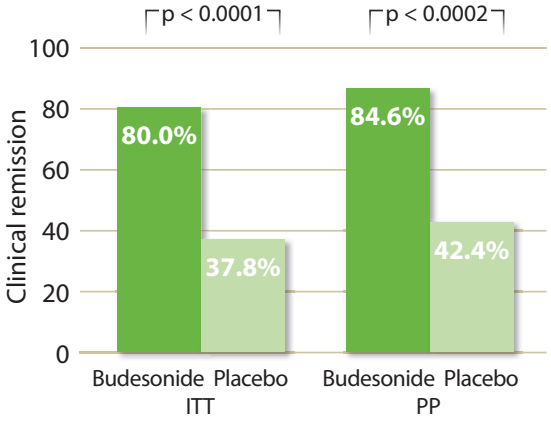
- Intermittent or persistent, also nocturnal watery diarrhoea for several weeks (stool frequency ≥ 3 per day)
- Commonly over 50 years of age
- Predominently women
- Accompanying abdominal pain
- Faecal incontinence complaints
- Smokers
- Concurrent medication (PPI, (lanzoprazole), SSRI (sertraline), NSAID, acarbose, ranitidine and ticlopidine)
- Concurrent autoimmune diseases (rheumatism, thyroid disease, diabetes, coeliac disease)

Further diagnostic investigation with colonoscopy and biopsies in the complete colon for histopathological assessments are required to make a diagnosis or to exclude microscopic colitis.

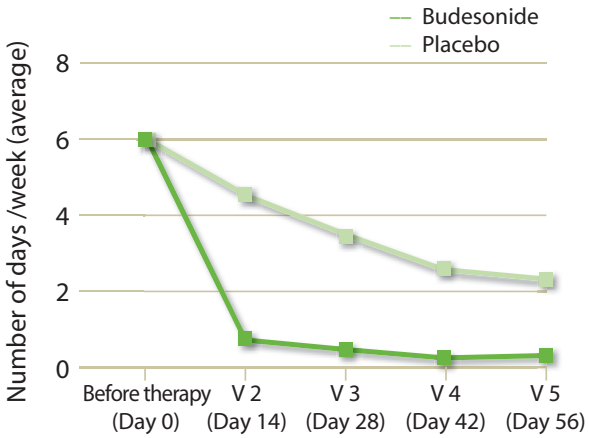
Figure 5. Checklist: When should microscopic colitis be considered?

80% of patients with collagenous colitis respond to treatment with budesonide.

Clinical remission
(Hjortswang criteria: On average < 3 bowel movements per day, of these < 1 watery stool per day)



Stool consistency
(Number of days with watery stools in the week prior to visit; ITT)



Budenofalk® 3mg capsules and Budenofalk® 9mg granules are the only pharmaceuticals approved for treating patients with collagenous colitis.
Budenofalk® (9 mg/day) is registered for the acute treatment of collagenous colitis for 8 weeks.
So far there is no registration for maintenance treatment.

Figure 6. Current study results on budesonide. Miehlke *et al*., Gastroenterology. 2012;142(Suppl 1):S-211, Abstr. No. 1158

susceptibility and there are supporting reports of familial occurrence. Seasonal variations in incidence also suggest that infection is an etiologic factor, although so far no definite association has been established with specific pathogens. It can reasonably be assumed that immunological factors also play a part, since around 40% of patients have a concomitant autoimmune disease. Dr. Pierik also emphasised that there is a clear association with use of certain drugs such as PPIs and NSAIDs. In terms of pathophysiology, there are also indications of bile acid malabsorption and myofibroblast dysfunction.

Huge Levels of Distress

Patients with microscopic colitis, according to Dr. Münch, have a hugely reduced quality of life in most cases: "Those affected are familiar with practically every toilet in the surrounding area." But it is not the high stool frequency so much as the stool consistency that causes the greatest distress. The watery stools very often mean a toilet must be found extremely quickly and, in surveys, around 40% of patients also report faecal incontinence. Nocturnal diarrhoea, which is inevitably associated with sleep disorders, also seriously impairs patients' quality of life. "Half of all patients with microscopic colitis report nocturnal diarrhoea as a problem," Dr. Münch said. In the majority of cases, patients report that they also suffer from abdominal problems including stomach cramp. This frequently involves unwanted weight loss and induces fatigue.

Budesonide Alleviates Symptoms and Improves Histological Findings

According to Dr. Münch, symptoms are unquestionably alleviated by treatment with the local steroid budesonide, as evidenced by the results of the BUC-63 trial. Here, budesonide achieves a significant reduction in stool frequency, an improvement in consistency and urgency in particular, as well as significant improvements in the concomitant abdominal complaints. In parallel, the number of days with faecal incontinence is clearly reduced and there is a sustainable improvement to quality of life.

Many Unresolved Questions Remain

Studies demonstrate that budesonide is highly effective clinically in collagenous and lymphocytic colitis, with remission rates of around 80%, Prof. Miehlke emphasised (Figure 6). The number-needed-to-treat (NNT) is "amazingly low" at just 2. Generally, once remission intervenes during treatment with budesonide, quality of life returns to normal and, in most cases, histology is also normalised. "But there are still many unresolved questions," Prof. Miehlke said. Studies are currently being conducted into maintenance treatment for patients who rapidly relapse symptomatically after cessation of budesonide and clearly require long-term treatment. And so far, there are no known treatment alternatives to budesonide, which means that treatment of patients that are non-responders or intolerant to budesonide remains an unresolved problem.

Information Material on Microscopic Colitis Designed by the European Microscopic Colitis Group (EMCG)

Microscopic colitis (MC) is a comparatively "new" disease and has yet to filter through into medical training and doctor's continuing professional development. Hence, physicians dedicated to the understanding of MC met in September 2010 in Stockholm, Sweden, to found the European Microscopic Colitis Group (EMCG). The primary objective of the EMCG is to create awareness of MC among patients, general practitioners, gastroenterologists, surgeons and pathologists regarding all aspects of MC, and to eliminate misconceptions. Another aim is to promote collaboration among the EMCG members in clinical trials and basic science. Evidence-based guidelines from the EMCG have recently been published (Munch *et al*., 2012, Microscopic colitis: Current status, present and future challenges: Statements of the European Microscopic Colitis Group. J Crohns Colitis). Find further information on microscopic colitis at www.emcg-ibd.eu

In a joint effort, the EMCG and the Falk Foundation e.V. provides comprehensive information material designed especially for gastroenterologists and pathologists, but also for non-specialist physicians and patients, with 3 separate leaflets on the subject.

Information Flyer
Microscopic Colitis for Gastroenterologists and Pathologists

Authors: D. Aust, S. Miehlke
6 pages (Bu15e)
This information leaflet produces information for both trained gastroenterologists and pathologists regarding the disease course of microscopic colitis, and the treatment options available.

Information Flyer
Microscopic Colitis

Authors: A. Madisch, S. Miehlke, A. Münch
6 pages (Bu14e)
This flyer provides comprehensive information for doctors on how to detect and effectively treat microscopic colitis and how to distinguish it from irritable bowel syndrome.

Patient Information
Frequent Diarrhoea? It Could be Microscopic Colitis!

6 pages (Bu85e)
This patient information leaflet offers clear, accessible information about microscopic colitis and the symptoms that it can cause. This leaflet aims to empower the sufferer and answer any questions that they might have about microscopic colitis and the treatment strategies that are available to them.

The leaflets can be downloaded as PDFs from the EMCG website (www.emcg-ibd.eu) or ordered free of charge from your local Falk partner. See www.drfalkpharma.com for contact details.

EMCG
European Microscopic Colitis Group

22nd UEG Week
18-22 October 2014
Austria Center Vienna (ACV)

UEG week 2014 will be held in the Austria Center Vienna (ACV) from 18-22 October.

UEG recognises that audience interaction is key to taking valuable knowledge, and so at the 22nd UEG Week there will be an increased focus on facilitating delegate interaction.

The programme for 2014 will feature a number of highlights, as well as some brand new features including:

The launch of a clinically oriented one-day symposium, entitled "Advances in Clinical Gastroenterology and Hepatology". This will focus on an area in which substantial progress has been made during recent years, and which has changed clinical practice. This symposium will deal with the increasingly active area of digestive oncology, where there is now substantially more to offer patients in terms of diagnostics and therapeutics as compared to previous years.

"Therapy updates". This session will focus upon the current state-of-the-art treatment options in some of the major GI and liver diseases, on irritable bowel syndrome, biologics in inflammatory bowel disease, gastroesophageal reflux disease, oesophageal cancer, therapeutic endoscopic ultrasound, and viral hepatitis.

The Role of Probiotics in the Prevention of Post-operative Crohn's Disease Recurrence

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Introduction

Complications of Crohn's disease (CD) such as strictures or fistulas or disease refractory to medical therapy leads surgery in around 70% of patients at 10 years.[1] Although surgery may be deemed "curative" at the time, endoscopic and clinical recurrence of the disease after ileo-colonic resection are common, and usually occur at the anastomotic site or within the distal neo-terminal ileum. Endoscopic recurrence rates are 73% at 1 year and 83% at 3 years,[2] and are predictive of future clinical recurrence. A number of medications have been investigated for their effect in reducing recurrence and benefit has been proven for short-term use of nitroimidazole antibiotics[3, 4] and long-term use of the immunomodulatory thiopurine drugs[5, 6] and mesalamine.[7] More recently, the biological agents infliximab and adalimumab have also proven highly effective at reducing endoscopic recurrence at one year and two years respectively.[8, 9]

The Role of Microbiota in Post-operative Crohn's Disease Recurrence

The efficacy of nitroimidazole antibiotics in the reduction of post-operative CD endoscopic recurrence suggests a role of gut microflora in this disease process. This is further substantiated by examining the influence that diversion of faecal stream and its reintroduction has on disease recurrence. In patients with a covering ileostomy after ileo-caecal resection, whereby faecal contents do not pass across the newly formed anastomosis, there is no endoscopic or histological disease recurrence at 6 months.[10] After closure of the ileostomy there is evidence of both endoscopic and histological recurrence at 6 months. Furthermore, this detrimental effect of faecal stream on neo-terminal ileal tissue has been shown to occur within 8 days of being infused across the ileo-colonic anastomosis.[11] This pivotal work presents compelling evidence that the faecal stream is an important influence in the pathway to disease recurrence.

Factors that may be involved in driving this inflammation include an increased bacterial burden and dysbiosis within the neo-terminal ileum. The small intestine is normally a micro-organism poor environment compared to the colon, which is more laden with micro-organisms. The loss of the ileo-caecal valve after ileo-caecal resection results in a bacterial exposure in the area of the anastomosis which is up to 800 times higher than samples taken prior to surgery.[12] After ileo-caecal resection there are higher levels of *Escherichia coli* present in ileal tissue compared to before surgery when cultured.[12, 13] Also there are also higher levels of the bacteria *Escherichia coli* and *Bacteroides*, upon culture, in those with endoscopic recurrence compared to those without.[12]

Faecalibacterium prausnitzii has been noted to be reduced in the ileo-colonic mucosa of IBD patients,[14, 15] and therefore this bacteria has also been studied in the post-operative CD setting. When surgical samples taken at ileo-caecal resection were analysed with Flourescent *In Situ* Hybridisation (FISH), it has been found that a lower number of *Faecalibacterium prausnitzii* at the time of surgery is associated with endoscopic recurrence at 6 months post-operatively. Also, endoscopic recurrence at 6 months was associated with a lower proportion of Firmicutes (i.e. *Clostridium coccoides* and *Faecalibacterium prausnitzii*) within samples taken at ileo-colonoscopy.[16] More recently we have noted that in those with severe endoscopic recurrence at both 6 and 12 months there are lower numbers of bifidobacteria compared with those with no or minimal recurrence.[17]

Probiotics for Prevention of Post-operative Crohn's Disease Recurrence

Probiotics are living, non-pathogenic microbes that, when introduced

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to the gut, are capable of benefiting the host. The long-term side effects of nitroimidazole antibiotics and concerns about the long-term use of biologicals and immunosuppressive medications make manipulation of the gut microbiota with probiotics an attractive option in combating post-operative CD recurrence.

There are a number of reports, which suggest that probiotics are effective in inflammatory bowel disease. *E coli Nissle 1917* has shown benefit in inducing and maintaining remission in Ulcerative Colitis(UC)[18, 19] and VSL-3 has also shown similar effects in UC[20] and is able to maintain remission in pouchitis patients.[21, 22]

In CD, the non-pathogenic yeast *Saccharomyces boulardii* has been found to be beneficial in a randomised trial assessing maintenance treatment in CD.[23] Further open-label trials of a combination of Bifidobacterium and Lactobacillus with a prebiotic[24] have shown efficacy at induction of clinical remission and the use of the probotic preparation *Lactobacillus GG* in a paediatric group has shown improvement in disease activity.[25] Further work with *Lactobacillus GG* assessing its effect on inducing and maintaining remission in a randomised trial failed to show benefit over placebo.[26] Similarly trials of *Lactobacillus GG*[27] and *E. coli Nissle 1917* failed to show benefit over placebo in randomised control trials assessing maintenance of disease remission. Overall, 2 Cochrane review papers have failed to demonstrate benefit for probiotics in either inducing[28] or maintaining[29] remission in CD.

In the prevention of post-operative CD recurrence benefit has been shown for the combination of antibiotics and probiotics compared with high-dose mesalamine. Here, patients were randomised to either receiving the antibiotic rifaximin 1.8g/d for 3 months followed by VSL#3, 6 g/day for 9 months (n=20) or mesalamine 4g/day for 12 months (n=20). Endoscopic assessment took place at 3 and 12 months with fewer patients with severe endoscopic recurrence being seen within the antibiotic/probiotic group as compared with the mesalamine group.[30]

Further larger scale studies have been undertaken to assess the effect of the probiotic *Lactobacillus jonhsonii* LA, at a dose of $4x10^9$ cfu, on the prevention of post-operative CD endoscopic recurrence.[31] Ninety eight patients were enrolled into this randomised placebo controlled trial with an endoscopic assessment taking place at 6 months after surgery. No differences were found between the two groups at 6 months. The same probiotic was also assessed in a further double-blinded placebo controlled study at a dose of 10^{10} cfu.[32] Endoscopic assessment took place at 12 weeks and, although a trend was visible in differences in numbers with severe endoscopic recurrence, there were no statistically significant differences between the two groups.

A further study has assessed the effect of *Lactobacillus GG* given for 1 year on endoscopic recurrence.[33] *Lactobacillus GG*, at a dose of 6 billion cfu twice daily, versus placebo was assessed in 45 patients. At the end of the study there were no significant differences in endoscopic recurrence at 1 year between the two groups.

A synbiotic regime of Symnbiotic 2000, combining 4 probiotic preparations, *Pediacoccus pentoseceus*, *L. raffinolactis*, *L. paracasei susp paracasei 19* and *L. plantarum 2362*, with 4 fermentable prebiotic fibres, was assessed in a placebo-controlled trial involving 30 patients. Endoscopic and clinical recurrence was assessed at the end of the 24-month study period, but no differences were noted between placebo and the active treatment group.[34]

Conclusions

The clinical trials on the use of probiotics in the prevention of post-operative CD recurrence have, on the whole, been disappointing, and when assessed with a meta-analysis show no benefit over placebo.[7] The benefit seen with the long-term treatment of rifampicin followed by VSL-3 over meslamine is open to interpretation in various ways. Benefit extending to 12 months has previously been noted when nitrimidazole antibiotics were given for 3 months post surgery,[4] but these antibiotics were evaluated against placebo. The combination of rifampicin and VSL-3 was however evaluated against mesalamine, which is known to have some beneficial effect in itself against post-operative CD recurrence,[7] and so one could postulate that the results are more notable. There may also be benefits in the combination of probiotics within VSL-3 rather than single stains, as preparations with greater than one strain have been of benefit in CD.[24]

Probiotic preparations appear to have more favourable effects in ulcerative colitis compared to CD in the data published to date. It is also important to note that in the majority of studies undertaken on the use of probiotics in CD, a large proportion of patients had ileal involvement rather than colonic disease.[35] There may therefore be differing effects of probiotics dependent on the site of disease. Certainly there would appear to be evidence to suggest a relevant dysbiosis in the neo-terminal ileum of post-operative CD patients. There is additionally decreased expression of paneth cell defensin proteins in CD ileal mucosa compared with colonic tissue, thereby altering the antimicrobial properties within these areas.[36] To assess further the differences between ileal and colonic responses to probiotic preparations, dendritic cell cytokine expression in response to *in vitro* incubation with probiotics has been assessed. The probiotics *L.Casei* and *Bifidobacterium Longum*, both components of VSL-3, failed to show significant modulatory effects on ongoing cytokine production from ileal dendritic cells after overnight incubation. Lactobacillus Casei had a greater effect on the production of the Interferon-gamma (IFN-γ) and Transforming growth factor beta (TGF-β) from colonic derived dendritic cells as compared with ileal derived dendritic cells.[37] It is also known that

the small intestine is more immunologically active as compared with the large intestine which may be contributory to inflammation being more focused within the neo-terminal ileum in the setting of post-operative CD recurrence.[38]

Given the evidence currently available, there would be no suggestion that probiotics are advisable for the prevention of post-operative CD recurrence. There would appear to be a difference in the efficacy of probiotics between ulcerative colitis and CD affecting the small intestine. Prior to further large scale clinical trials with probiotics, the underlying mechanisms of probiotics in each intestinal area may need further exploration. Additionally, targeting more specifically the microbiota that appear associated with post-operative CD recurrence may be of benefit.

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Transmural Healing in Crohn's Disease

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Crohn's disease (CD) is a chronic and frequently progressive inflammatory bowel disease often associated with poor quality of life and disability for affected individuals.[1, 2] The persistent transmural inflammation that typifies CD frequently determines structural bowel damage and intestinal complications such as strictures, fistulae and abscesses; these often require resective surgery, which itself adds further disability and loss of quality of life.[3, 4]

The recent scientific production focusing on treatment of CD has shown that mucosal healing (MH) can be achieved mainly through therapeutical management by biologics, and that it represents a crucial end-point in CD patients, being a predictor of lower need for steroids, hospitalisation and surgery in the years following treatment.[5, 6] As a consequence, MH has been used as an outcome measure in numerous clinical trials[7, 8] and has been shown to predict maintenance of clinical remission. In addition, some reports have highlighted lower healthcare costs for those patients who achieve MH compared to those who do not.[9, 10]

Moving from considerations, in recent years the concept of "deep remission" for CD patients treated with biologics/immunosuppressors has been proposed.[11, 12] Although firm consensus on terminology is not available, at present the definition of deep remission can be applied to CD patients in stable steroid-free clinical remission with no biochemical and endoscopic signs of bowel inflammation.[13, 14] In accordance with the importance of deep remission as a prognostic factor for CD management, a recent study has shown that it is a pivotal factor that can also orient the decision-making around withdrawal of biologic therapy in the long-term.[15]

On the other hand, as mentioned above, CD is characterised by transmural inflammation and it is not clear if MH corresponds to healing of the entire bowel wall. The occurrence of what we usually define as "transmural healing" (TH) in CD patients treated with anti-TNF alpha (and/or other drugs) has, to our knowledge, been explored in a very limited number of studies.[16, 17] The main limitation in exploring the occurrence of TH is mainly represented by the lack of a diagnostic gold standard. In effect, the degree of transmural inflammation and any changes that may indicate its healing cannot be studied histologically in patients who do not undergo surgery, even if, at least in our mind, we can postulate that a CD patient without mucosal inflammation at endoscopy and with no signs of inflammation at cross-sectional study can be considered macroscopically "healed".

This kind of diagnostic limitation applies to all cross-sectional tools we could use (CT, MRI, ultrasonography), making the assessment of transmural changes achievable only indirectly. In effect, there are no validated cross-sectional tools for defining TH of the bowel wall in CD even if a number of reviews and meta-analyses[18, 19] have highlighted the high diagnostic accuracy (>90%) of CT, MR-enterography and ultrasonography (US) for the diagnosis of CD. In this particular field, a recent study carried out by our group directly compared the diagnostic accuracy between US and MR-enterography and showed that US is not inferior to MRI for the diagnosis of small bowel CD, with the advantages of availability and limited cost.[20] On the basis of these findings, we used BS for the detection and follow-up of TH in CD.

Starting from these considerations, and despite the aforesaid diagnostic limitations, we recently performed a study exploring the rate of TH, assessed by US, in 133 CD patients after a 2-year period of treatment with biologics or thiopurines.[21] Interestingly, we were able to show that TH can be achieved in about 25% of CD patients on maintenance treatment with biologics and in a much smaller proportion of patients (4%) treated with traditional immunosuppressors (Figure 1). The variables that were significantly associated with TH were the pre-treatment endoscopic score and duration of CD. In effect, a lower basal endoscopic score and a shorter duration of disease were associated with the best response to anti-TNF alpha agents in terms of TH. Furthermore, good agreement was found between TH and MH (k=0.63). On the contrary, poor agreement was found between TH and clinical remission (k=0.27) while good concordance between TH and C reactive protein levels was underlined (k=0.79;p=0.02). When considering CD behaviour, only 1 out of 16 patients with strictures (6%) and no patient with penetrating CD achieved TH. The results shown in our paper were well-correlated with the initial study by Paredes *et al*. showing US normalisation in 5 out 24 CD patients (20%) treated by anti-TNFs.[16]

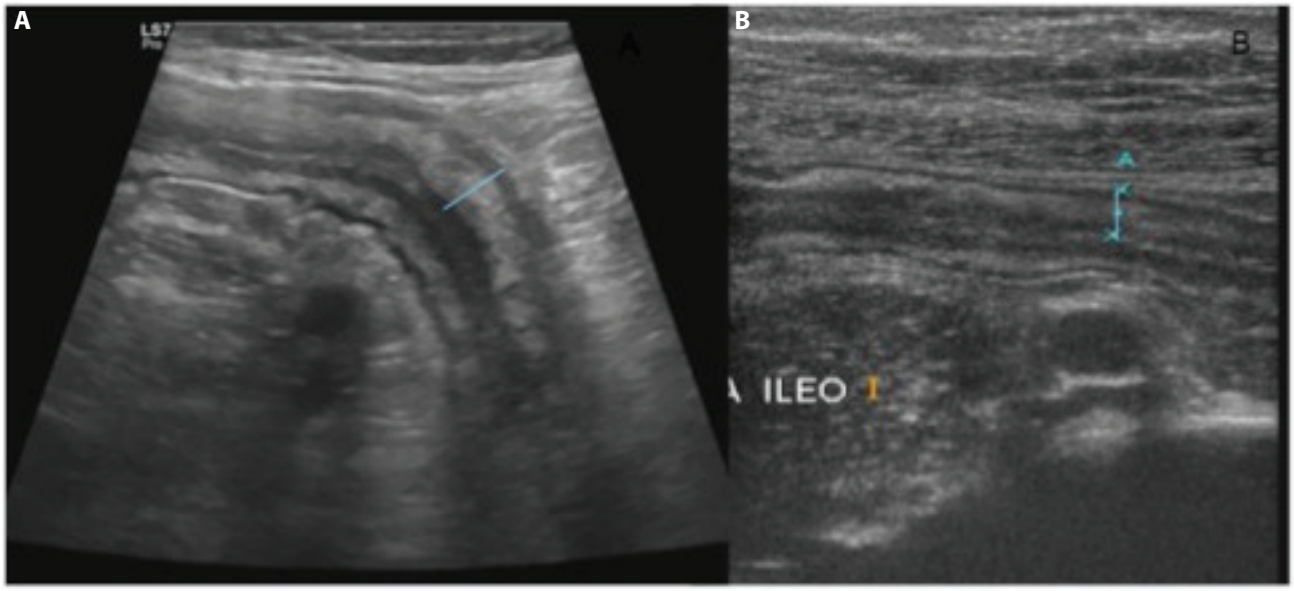

Figure 1. TH: US picture at baseline (A. bowel wall thickness 7 mm) and after 2 years of treatment with biologics (B. bowel wall thickness 3 mm).

More recently, Van Assche *et al*. reported a study about the effects of infliximab on transmural lesions as assessed by MRI-enteroclysis in 20 patients with ileal CD.[22] The MRI index improved in 44% at week 2 and in 80% at week 26 while complete absence of inflammatory lesions, that we could consider a surrogate parameter of TH, was observed in 0/18 at week 2 and 13% (2/15) at week 26. Interestingly, the obstructive elements (i.e. the bowel strictures with the highest transmural inflammatory involvement) did not change, indirectly confirming that "early CD" tend to react better to the therapy in terms of TH.

However, the main finding of these studies was the fact that, at least potentially, biologics can induce TH in CD, thus restoring the affected bowel to its pre-disease condition, as well as its macroscopic structure. This can be considered a great success for the evolution of medical treatment of CD. It is possible that the efficacy of anti-TNF alpha agents compared to that of traditional drugs (e.g. thiopurines) with respect to this outcome is the result of a specific biological effect of anti-TNF alpha agents on the inflammatory mechanisms in the deep layers of the bowel wall (e.g. sub-mucosal inflammation, fibrosis).[23] In truth, recent studies have shown that infliximab can stimulate regulatory macrophages - which have the ability to induce wound healing in an *in vitro* model - thus suggesting a key role for this cell population in MH and, possibly, TH.[23]

As reported, recent studies have highlighted that patients in deep remission show low risk of recurrence after suspension of treatment with biologics.[15] Hence, CD patients with evidence of TH on biologics may have better prognostic factors. However, further studies assessing the usefulness of TH as an additional parameter in decision algorithms around the suspension of treatment with biologics are necessary. In this sense, TH could provide and additional prognostic element in defining what is the real significance of "deep remission" in CD.

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Sedation in Screening Colonoscopy increases Coecal Intubation Rates but not Detection Rates during Screening Colonoscopy

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The impact of sedation on detection rates during colonoscopy is still controversial, although sedation during screening colonoscopy is increasingly used. In an article by Bannert *et al*.[1] cecal intubation rate (CIR) in the general population (52.506 screening colonoscopies) increased from 94.3% without sedation to 95.8% under sedation. Although sedation was used more frequently in women (91%) then in men (82%), in female patients the use of sedation increased the CIR by about 3% (from 92% to 95%), and in men only by 1.3% (from 95.5% to 96.8%). However, even if women underwent endoscopy under sedation, the CIR was not higher than in unsedated men (94.96% vs. 95.53%; p=0.1005). This increase in CIR had no impact on overall adenoma detection rates, which were 15.8% in unsedated and 15% in sedated women, and 25.4% in unsedated and 25.3% in sedated men, respectively. Particularly in women, the increase of cecal intubation rates due to sedation did not increase the adenoma detection, probably related to a generally lower adenoma prevalence in women.[2]

Accordingly, in a recent publication coecal intubation rates had no impact on occurence of interval cancers.[3] Sedation may allow examiners to inspect the mucosa more closely and therefore may have an impact on performance quality. However flat polyps were found more frequently in unsedated patients in the study of Bannert *et al*. In sedated patients, due to lacking reports of pain, higher amount of air can be insufflated. Thus, flat polyps may appear less. On the other hand, if the patient is sedated, the endoscopist has probably more time to aspirate air and sedation may allow a closer inspection of the mucosa in sigma or rectum, as polyps in this location were found more frequently in sedated men.[1] Since position changing during withdrawal increases adenoma detection rate,[4] sedation can have a contrary effect. A patient who is awake can change position more easily than one in deep sedation.

Recommendations for screening colonoscopies include an ADR over 25% for men and 15% for women.[5] The most important finding in this large cohort study[1] is that sedation has no influence on overall polyp or adenoma detection rate. In contrast, in a study where colonoscopies regardless of indication were included, Radaelli *et al*. found that benzodiazepine alone and propofol increased the probability of polyp detection with an odds ratio of 1,17.[6] However, they reported a low sedation rate of 55.3%, which may reflect a distinct patient selection for sedated colonoscopy. Furthermore the cecal intubation rate and PDR differed according to indication, with a CIR of 86.0% and a PDR of 24.2% in screening colonoscopies, which is probably below a recommended threshold for ADR. It is reasonable, that if sedation is only administered in selected patients, PDR may improve under sedation. Bair *et al*. reported an ADR of 25.47% and a PDR of 46.11% in screening colonoscopy under sedation,[7] other groups found an ADR of 22-24%[8-10] and a PDR of 38-43%[9-11] in screening colonoscopies with variable sedation.

Although the risk-benefit-ratio of sedation has been controversially discussed,[12] it has become common practice in endoscopic procedures[13, 14] in the past years. Sedation reduces patient discomfort and pain, and leads to increased operator satisfaction.[15] Recently it has been shown that sedation does not result in a significantly increased rate of cardiovascular or respiratory complications.[16] Findings from an Italian study imply that pre-medication may result in a higher probability to reach the cecum. Data analysis from 12825 colonoscopies showed a cecal intubation rate of 76.1% in unsedated procedures vs. 84.2% in procedures with sedation, with influence of the endoscopist's colonoscopy volume on the likelihood of reaching

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the cecum.[6] Other studies provided higher rates of cecal intubation under sedation with values ranging from 93.33 to 100.00%,[7, 16, 17] within the recommended quality standard.[5]

It is still unclear if the use of sedation increases participation rates in screening programmes. In a 2005 performed questionary in Austria only 24% of patients had no anxiety regarding colonoscopy, whereas 48% had "small anxiety" and 24%" big anxiety". Accordingly, 86% of screening colonoscopies in Austria are performed under sedation.[18]

In conclusion, sedation in colonoscopy is safe, it increases cecal intubation rates but has no impact on detection rates. It can be used to minimise patients anxiety to screening colonoscopy and therefore may lead to increasing participation rates in screening programmes.

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Colon Capsule Endoscopy: Can Moviprep® be used as Bowel Preparation as well as Booster? Observation Study in 95 Patients

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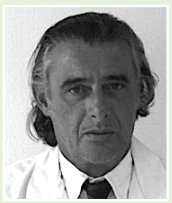
Introduction

Pillcam colon capsule endoscopy (CCE) enables colic visualisation without the need of general anesthesia (Given Imaging, Ltd, Yoqnéam, Israel). It includes a CMOS system (complementary metal oxide silicone) which captures 2 images per head and per second, a battery and an ASIC system (Application specific integrated circuit) including a radio-frequency transmitter with a LED-type lightening (White light emitting diode). This technique requires a long enough battery life to perform an entire colonic recording as well as an excellent bowel preparation. Similarly to colonoscopy, preparation includes a low-residue diet several days before, with most of the time 4 litres of PEG (polyethylene glycol).[1,2] During CCE, capsule propulsion should be boosted in the colon once it has entered the small intestine. Fleet® (sodium phosphate) (Table 1) is used in most of the studies, yet Fleet® can be contra-indicated in some cases.[3] The goals of this study was to assess the quality of the bowel preparation with 2 litres of Moviprep® (PEG + ascorbic acid + ascorbate and Na sulfate) and its efficacy as booster when substituted to Fleet®.

Material and Method

Patients

This prospective observation study was carried out from November 2009 through December 2012 in 95 consecutive patients, refusing general anesthesia despite its insightful information on colonoscopy indication.



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Eighty five CCE were used in 44 females and 51 males, with a mean age of 58 ±3 (range 16 to 84): 55 first generation CCE1 and 40 second generation CCE2 (5 patients with a contraindication to anesthesia, 8 patients with anticoagulant therapy, 13 patients with antiplatelet treatment).

Capsule Endoscopy

First generation CCE size 1 is similar to the size of the small bowel capsule (31 mm long and 11 mm in diameter), with a field of view per head of 156°. It stops recording after 5 minutes and then automatically starts again after 105 minutes (1h45) to finally stop recording at 600 minutes (10 h). Direct visualisation of the GI tract can be performed thanks to a laptop and the "Rapid access" software.

Second generation CCE2 is slightly bigger (31.5 mm long and 11.6 mm diameter), with a larger field of view per head of 172°. It switches off after 3 minutes, records 14 images per minute and starts recording again according to an algorithm which detects the small intestine between 30 and 120 minutes after ingestion, then switches off between 600 and 900 minutes (10 to 15 hours). CCE2 records from 2 to 15 images per second and per head depending on speed progression in the colon. Continuous visualisation of the GI tract is performed using the DR3 hardware, and "Rapid 7" version allows polyps size assessment in millimeter as well as their spectral analysis with FICE (Fuji intelligent chromo endoscopy).[4]

There is a significant difference ($p < 0.0001$) in colonic transit times between group 1 and 2, using the Student test.

Bowel Preparation

3 days before the examination, all patients followed a low-residue diet and any iron therapy was stopped about ten days before. All of them had a bowel preparation based on an amended "standard" protocol[1-3] with 2 litres of Moviprep® the day before or the morning of the examination, depending on the ingestion schedule (8.00 a.m. or 11.30 a.m.) and the "booster" varied according to two consecutive periods: period A, the first 70 patients included received Fleet® as a "booster"

"Standard" Protocol	Protocol #1	Protocol #2
D5 to D2 Low-residue diet	D5 to D2 Low-residue diet	D5 to D2 Low-residue diet
D2 Intake of 2 L of clear liquids Sennosides 4 tablets in the evening	D2 Intake of 2 L of clear liquids Sennosides 4 tablets in the evening	D2 Intake of 2 L of clear liquids Sennosides 4 tablets in the evening
D1 07.00 am- 7.00 pm: clear liquids 7.00 pm- 9.00 pm: 3 or 2 L of PEG	D1 07.00 am- 7.00 pm: clear liquids 7.00 pm- 9.00: pm 2 L of Moviprep®	D1 07.00 am- 7.00 pm: clear liquids
D Day 06.00 am – 07.00 am: 1 or 2L of PEG (4 L in total) 07.45 am: 1 tablet domperidone 20 mg 08.00 am: PillCam Colon ingestion 10.00 am: Booster 1 30 to 45 mL Fleet® + 1L water 2.00 pm: Booster 2 15 to 30 mL Fleet® + 1L water 4.30 pm: bisacodyl suppository (10 mg) if capsule is not ejected	D Day 07.45 am: 1 tablet of domperidone 20 mg 08.00 am: PillCam Colon ingestion 10.00 am: Booster 1 45 mL Fleet® + 1L water 2.00 pm: Booster 2 22.5 mL Fleet® + 1L water 4.30 pm: bisacodyl suppository (10 mg) if capsule is not ejected	D Day 06.00 am – 07.00 am: 1 L of Moviprep® (+ 1 L Water) 08.00 am - 10.00 am: 1 L of Moviprep® (+ 1 L Water) 11.00 am: 1 tablet of domperidone 20 mg 11.30 am: PillCam Colon ingestion 1.30 pm: Booster 1 0.5L Moviprep® (+ 0.5L H20) 5.00 pm: Booster 2 0.5L Moviprep® (+ 0.5L water) 6.30 pm: 10 mg bisacodyl suppository if capsule is not ejected

Table 1. Preparation protocols to perform a colon capsule endoscopy.

(protocol #1); period B, the last 25 patients received Moviprep® as a "booster" (protocol #2).

Protocol #1 (70 patients): low-residue diet (D5 to D2), pursenide (D2), clear liquid diet and 2L of Moviprep® on D1, capsule ingestion at 8.00 a.m., booster #1 with 45mL of Fleet® 2 hours later and booster# 2 with 22.5mL of Fleet® 6 hours after ingestion if the capsule had not been egested.

Protocol #2 (25 patients) : low-residue diet (D5 to D2), pursenide (D2), clear liquid diet on D1, 2L of Moviprep® the morning of the examination, capsule ingestion at 11.30 a.m., booster #1 with 500mL of Moviprep® 2 hours later and booster #2 with 500mL of Moviprep® 6 hours after ingestion if the capsule had not been egested.

Examination

Once the cutaneous electrodes had been placed, the hardware control and its CCE recognition had been performed, procedures were performed early or later in the morning according to periods A and B. The capsule was ingested with 25 mL of cold water.

Egestion rate was evaluated in both groups as well as the quality of the bowel preparation according to 4 grades (excellent, fair, average, poor) later summarised by 2 items: adequate (excellent/fair) or inadequate (average/poor).[5]

Recordings were all read and analysed by the same investigators (JC.L, P.AL, M.C) following a 3-step reading: a. reading in "Quick view" mode forward and backward to define the anatomical landmarks; b. normal mode forward reading with backward or targeted reading using one or 2 heads on a lesion (7 to 15 images per second). All digestive lesions viewed during the examination were reported.

Recording times were collected on all patients, from the mouth to the Bauhin valve (oro-caecal transit time) and from the caecum to the anus (bowel transit time). Student Test was used to perform all of the statistical comparisons of these data.

Results

No ingestion-related failure, as well as no complication related to the bowel preparation or the device was recorded. Only 3 patients called the secretariat for further information. Hardware was returned to the secretariat in the evening or the day after the examination, all undamaged.

In the group including 70 patients with preparation protocol #1 (55 CCE1 and 15 CCE2), 60 examinations were rated complete (85.7%), 10 incomplete (14.3%) including 5 cases of sigmoid retention, 4 cases where the rectum was difficult to analyse due to dark rectal residual liquids and one case of premature recording termination in the ascending colon. Preparation was rated adequate in 59 patients

(84.2%). Mean colic and oro-caecal transit times were respectively 2 hours 47 min and 3 hours 22 min.

In the group including 25 patients with preparation protocol #2 (25 CCE2), 13 examinations were rated complete (52%), 12 incomplete (48%) including 7 cases of sigmoid retention and 5 cases where the rectum was difficult to analyse due to dark rectal residual liquids. Preparation was rated adequate in 14 patients (56%). (Ascending colon 64%, transverse colon 64%, descending colon 68% and rectum 34%). In this group, CCE expulsion occurred in less than 6 hours in

Authors	Year	Patients	Adequate preparation (excellent/ fair)	Complete bowel examination	Detection rate of colonic polyps	Type of preparation
Gay[4]	2009	128	81.7%	90.5%	53.2%	Bowel preparation: 3+1 L of PEG Booster 1: 45 mL Fleet® Booster 2: 30 mL de Fleet®
Eliakin[7]	2009	104	78%	81%	44%	Bowel preparation: 3+1 L of PEG Booster 1: 45 mL Fleet® Booster 2: 30 mL de Fleet®
Sacher Huvelin[9]	2010	545	52%	91%	46%	Bowel preparation: 3+1 L of PEG Booster 1: 45 mL Fleet® Booster 2: 30 mL de Fleet®
Spada[6]	2011	117	81%	88%	41.3%	Bowel preparation: 2+2 L of PEG Booster 1: 30 mL Fleet® Booster 2: 20 mL de Fleet®
Spada[3]	2011	20	53%	75%		Bowel preparation: 3+1 L of PEG Booster 1: 500 mL of PEG Booster 2: 500 mL of PEG
		20	35%	100%	3.52%	Bowel preparation: 3+1 L of PEG Booster 1: 45 mL Fleet® Booster 2: 30 mL de Fleet®
Letard	2012	70	84.3%	86%	45.7%	Bowel preparation: 2 L Moviprep® Booster 1: 45 mL Fleet® Booster 2: 25 mL de Fleet®
		25	56%	52%	32%	Bowel preparation: 2 L Moviprep® Booster 1: 500 mL Moviprep® Booster 2: 500 mL de Moviprep®

Table 2. Results on preparation quality, complete or incomplete examination and number of colonic polyps depending on the various types of preparations.

27% of cases, in less than 8 hours in 19% of cases and in more than 10 hours in 54% of cases or it was blocked in the sigmoid. Mean colic and oro-caecal transit times were respectively 3 hours 03 min and 6 hours 07 min. Due to insufficient preliminary results, protocol #2 had to be prematurely stopped.

There is a significant difference ($p < 0.0001$) in colonic transit times between group 1 and 2, using the Student test.

Nine out of 40 CCE 2 had a recording time superior to 12 hours, with a maximum recording time of 17 hours 53 min in one patient.
139 lesions were identified in 53 patients (56%) (7 esophagitis, 13 gastritis, 8 lesions of the small intestine, 24 diverticulosis , 1 ischemic colitis, 2 caecal angiodysplasia, 2 inflammatory bowel disease, one colic melanosis, 81 colic polyps larger than 5 mm in 40 patients (32 in protocol #1 and 8 in protocol #2).

Once the CCE was completed, further endoscopic examinations were recommended to 44% of patients: 6 esogastroduodenal fibroscopies, 7 recto-sigmoidoscopies and 24 colonoscopies. Considering the obtained results, the prescribed endoscopies were performed in most of the patients (5 persistent refusals of the anesthesia).

Discussion

In this study, CCE seemed easy to perform no matter when it was ingested in the morning. No ingestion failure of CCE1 or CCE2, nor device damage or any other preparation or medical device related complication was observed despite the slightly larger size of the second generation. Patients understood fairly well the examination, with only 3.3% calling back our secretariat for further information. In Spada *et* Eliakin study, 6.8 to 8% of patients suffered from nausea, vomiting, headaches or abdominal pain, 24 to 48 hours following the examination, and could most of the time be preparation-related.[6, 7]

When performing a CCE, bowel preparation is critical, as residues can't be rinsed out. Initially, the preparation protocol included 4 litres of PEG (3 litres the day before and 1 litre the morning of the examination), whereas currently 2 litres of PEG the day before and 2 litres the morning of the examination are preferred. Results from various authors sometimes differ, with an adequate preparation rate ranging from 52 to 81.7%, with a complete examination rate when associated to Fleet® as a booster ranging from 81 to 91% depending on series.

In our study, when 2 litres of Moviprep® was given the day before the examination, adequate preparation rate was 84.2% and complete examination rate was 85.7%. Bowel transit times were 3 hours 22 min on average, slightly superior to transit times with 4 litres of PEG preparation reported in the literature.[3, 4]

Booster is essential, as there are few longitudinal contractions in the colon. CCE propulsion is thus required. The booster goal is to accelerate CCE in the small intestines and then in the colon before the battery stops. In fact, Sieg *et al*. tried to stop giving a booster, and their egestion rate after 6 hours decreased from 84 to 0%.[8] However, Fleet® can be sometimes contraindicated, as it can induced an acute nephropathy with kidney failure.

In our study, and when Moviprep® was used as a booster, only 56% of preparations were rated adequate and examinations were only complete in 52% of cases, with a major increase of bowel transit time to 6 hours 07 min on average, similarly to Spada *et al*. results where mean bowel transit time was 5 hours 32 min in case of PEG use as a « booster ».[3]

In our patients, the number of colonic polyps visualised with CCE was 42% for both protocols, with yet 45.7% with regards to protocol #1 and 32% with regards to protocol #2 where preparation and CCE progression were insufficient (Table 2). These results are similar to the results published in the literature, and vary from 41.3 to 53.2% depending on the type of bowel preparation and transit time.[3, 4, 6, 7, 9, 10]

In our patients, other lesions could be visualised, further leading to a GI endoscopy in 44% of them, with few of them refusing anesthesia once lesions had been visualised (5%).

Conclusion

In patients for whom 4 litres of PEG in-take to perform a CCE is impossible, a bowel preparation with 2 liters of Moviprep® the day before is associated with fair quality examination in 84.2% of adequate preparations and a complete bowel examination in 85.7% of cases, if Fleet® is associated as a booster.

In contrast, Moviprep® as booster, similarly to PEG, is less efficient on bowel peristalsis than Fleet®, twice as long bowel transit times.

Future discussion could include Fleet® dosage to be prescribed for phases 1 and 2 of the booster.

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Endoscopic Surveillance in Attenuated Polyposis

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Introduction

Until approximately 1990, colorectal polyps were classified into two groups: adenomatous polyps and hyperplastic polyps, with the latter thought to have no risk of malignant transformation. Conventional adenomas are the main precursor lesions to colorectal cancer (CRC) developing via the traditional adenoma–carcinoma pathway, which is characterised by chromosomal instability. Instead, 'hyperplastic polyps', now referred as serrated polyps, are in some cases associated with an increased risk of developing advanced neoplasia and CRC.[1-3] These lesions have a risk of malignant transformation through the serrated neoplasia pathway, characterised by BRAF mutation and CpG island methylator phenotype, with or without microsatellite instability.[4] Adenoma endoscopic resection has proven its efficacy in reducing CRC incidence and mortality in large prospective studies.[5, 6] However, this effect has not been proven in serrated polyps. Furthermore, due to their characteristics, serrated polyps are difficult to detect and have an increased risk of residual disease after endoscopic resection.[7]

Attenuated polyposis syndromes are defined as the presence of 10 to 100 colon polyps detected during one or more endoscopies and are associated with an increased risk of CRC. These syndromes are defined on the basis of the familial history, polyps' histology and underlying genetic alterations.[8-12] While in classical familial adenomatous polyposis (FAP) endoscopic follow-up only allows the detection of polyposis and determines when to perform prophylactic surgery; in attenuated polyposis syndromes endoscopic surveillance and resection of the detected lesions may reduce the risk of developing CRC and the need for surgery.[13] In fact, the risk of detecting a CRC or requiring surgery is directly related to the findings of the initial endoscopy, and this risk is clearly reduced during follow-up.[14, 15]

Our aim is to review the available evidence on this subject and define which are the surveillance recommendations based on the phenotype and the underlying molecular alterations.

Attenuated Adenomatous Polyposis (AAP)

AAP syndromes are a heterogeneous group with similar endoscopic phenotype, but with different genetic characteristics and CRC risk. Two genetic alterations account for most of the inherited AAP: APC and MUTYH as well as for a variable percentage of the AAP without a family history (Figure 1).

Definition, Genetics and Natural History

Attenuated familial adenomatous polyposis (AFAP) is defined on the basis of the criteria proposed by Nielsen *et al*.:(a) at least two first-degree relatives with 10–99 colorectal adenomas diagnosed after the age of 30 years, (b) one patient with 10–99 adenomas diagnosed after 30 years plus a first-degree relative with CRC and a few (<10) adenomas, and, applying for both criteria, (c) no family members with "classic FAP" before 30 years.[16] APC or biallelic MUTYH mutations are found in 70-72% of the families that meet these criteria.[16, 17] A multiple colorectal adenoma (MCRA) phenotype is defined in individuals who do not meet these criteria independently of familial history.[12, 17] Based on this classification, individuals who do not meet AFAP criteria have a lower risk of APC or MUTYH mutations.[18] On the other hand, a recently published cross sectional study has shown that adenoma count was strongly associated with a pathogenic mutation in multivariate analyses. In this sense, a pathogenic mutation in APC or MUTYH was detected in 10% and 7% of the individuals with 20-99 adenomas and in 5% and 4% of the individuals with 10-19 adenomas independently of family history.[18]

In individuals with AAP associated to APC mutations, diagnosis is made at a mean age ranging from 35 to 45 years, and CRC diagnosis is made at a mean age of 55 years. Knudsen *et al*. described a 69% cumulative risk of CRC by the age of 80 years.[19] In comparison with FAP, polyps are mainly located in the proximal colon and there is a 15 years delay in the age of CRC onset when compared with FAP.[13, 20, 21] In individuals with AAP associated to biallelic MUTYH mutations (MAP), diagnosis is made at a mean age ranging from 45 to 56 years[22] and the risk for CRC is high. Up to 60-70% of MAP CRC patients were first diagnosed at a mean age of 47 years, and CRC is present in about 50% of individuals at the time of polyposis diagnosis.[21] Both genetic alterations produce an indistinguishable phenotype in terms of colonic manifestations.

In contrast, individuals with AAP without genetic mutations differ

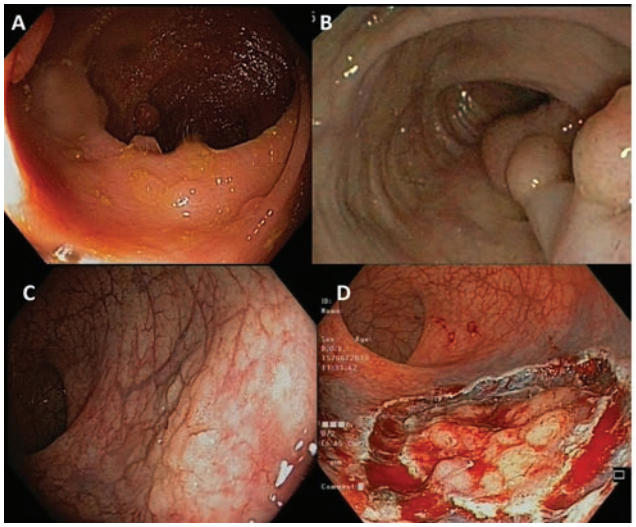

Figure 1. Attenuated adenomatous polyposis. A and B. Multiple protruded lesions in individuals with attenuated adenomatous polyposis without pathogenic mutations in APC or MUTYH; C. Flat elevated lesion in a patient with MUTYH adenomatous polyposis; D. Endoscopic submucosal dissection of the previously shown lesion. Histology revealed a tubulovillous adenoma with high grade dysplasia.

from those with genetic mutations. In the study published by Filipe *et al*., AFAP without mutations had a lower number of adenomas (i.e., presence of less than 30 adenomas 83% vs. 11.5%) and a lower frequency of CRC (17% vs. 45.4%). Besides, individuals with MCRA phenotype without genetic mutations presented significant differences when compared with individuals with MCRA with MUTYH mutations. Accordingly, they were characterised by a later age of onset (range 35–75 vs 23–69), lower polyp multiplicity, (i.e., presence of less than 30 adenomas 75% vs 29%) and lower frequency of CRC (45% vs 71%).[17]

Surveillance

There are four issues to answer on AAP surveillance: how to perform endoscopic examination, when to start, how often and when is the moment that endoscopic follow-up is insufficient to control AAP. Only one study has evaluated different visualisation techniques in FAP.[23] In this study, chromoendoscopy detected the greatest number of lesions at all sites within the large intestine, and detected a significantly greater number than the other procedures on the left side of the large intestine. Narrow-band imaging (NBI) depicted a greater number of lesions than did white light in the transverse colon, descending colon, and rectum. Autofluorescence imaging showed a greater number of lesions than did white light in the rectum.

Patients with AAP with APC mutation should always be screened by colonoscopy because of the frequency of proximal colonic polyps. The screening should be performed every 1–2 years, beginning in the late teenage years or in the 20s.[24, 25] Approximately one third of these patients can be managed during the long-term with colonoscopy and polypectomy because of small polyp numbers.[15, 19] About 64-66% will eventually require colectomy, with ileorectal anastomosis. Annual post-operative rectal surveillance is required for polyp ablation, but subsequent proctectomy is rarely needed (Table 1).[25]

Patients with MAP often develop proximally located CRCs, so at-risk individuals should receive colonoscopic surveillance. As long as the diagnosis of CRC before the 30s is rare, screening should be started as recommended in individuals with APC mutations,[24] or in their mid-20s or mid-30s.[25] Subtotal colectomy is advised for patients who develop colon cancer and should also be considered when colonoscopic management becomes problematic (Table 1).[25]

In contrast, no clear recommendation has been issued on endoscopic surveillance in individuals without pathogenic APC or MUTYH mutations. Based on clinical data, these patients have a lower number of adenomas which makes complete endoscopic resection feasible. Besides, risk of developing CRC is lower and at a more advanced age.[16, 17] On the other hand, Thirlwell *et al*.[12] found no evidence for a specific mutation signature in tumours from these patients, suggesting similarities with the classical pathway of tumorigenesis in sporadic adenomas. So, after complete endoscopic resection, surveillance can be performed on the basis of the colonoscopic surveillance following adenoma removal recommendations.[26, 27] As an example, on the basis of the European guidelines, colonoscopy should be repeated within 1 year after complete adenoma removal and later at a 1, 3 or 5 year interval on account of the number of resected adenomas in the previous endoscopy.[26] In contrast, on account of US Multi-Society Task Force, a three year interval is recommended after complete endoscopic resection (Table 1).[27] To sum up, an individualised approach should be recommended for patients with large number of adenomas.

	Imaging technique	Start time	Frequency
Attenuated adenomatous polyposis with APC mutations	Chromoendoscopy	15-25 years	1-2 years
Attenuated adenomatous polyposis with MUTYH mutations	Chromoendoscopy	20-30 years	1-2 years
Attenuated adenomatous polyposis without mutations	Chromoendoscopy	After detection	On the basis of adenoma surveillance recommendations
Serrated polyposis syndrome	Chromoendoscopy or Narrow band imaging	After detection	1-2 years

Table 1. Surveillance recommendations in attenuated polyposis syndromes

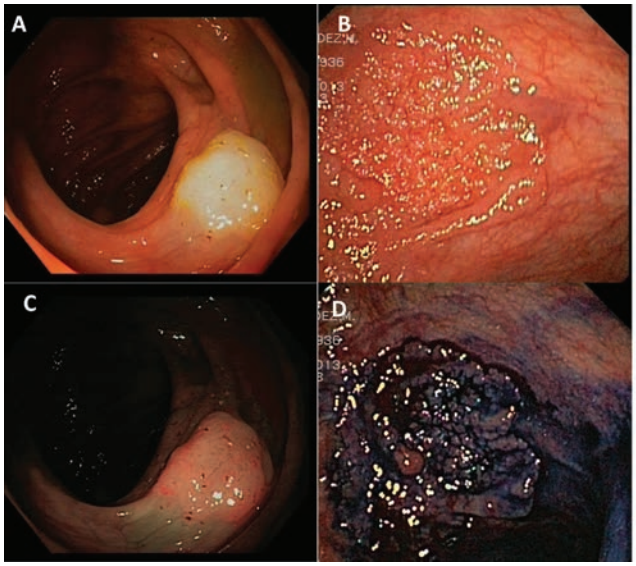

Figure 2. Serrated polyposis syndrome. A and B: Visualisation of a sessile and a flat elevated serrated adenomas with with white light. C and D: The same lesions evaluated with narrow band imaging (C) and chromoendoscopy with indigo carmin (D).

Serrated Polyposis Syndrome

Definitions and Natural History

SPS is a relatively rare condition characterised by multiple and/or large serrated polyps of the colon. Diagnosis of this disease is made by the fulfillment of any of the World Health Organization's (WHO) clinical criteria: at least five serrated polyps proximal to the sigmoid colon, two of which are greater than 10 mm in diameter; any number of serrated polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis or more than 20 serrated polyps of any size distributed throughout the colon.[28] SPS has an increased risk of CRC, which occurs from 50 to 60 years. CRC shows a trend to be located in the proximal colon. The mean age at diagnosis is 55 years. The pattern of inheritance is unknown and 10-50% of patients meeting SPS criteria have a family history of CRC.[3, 29–31]

Diagnosis and Treatment

Serrated and hyperplastic polyps present specific endoscopic findings. Hyperplastic polyps appear pale, glistening, and very similar to the surrounding mucosa and usually covered by mucus. The vascular network is weak, in contrast to that of hypervascular adenomas. In addition, serrated polyps, mainly sessile serrated polyps (SSP), are typically sessile or flat, making their detection even more difficult.[30] The miss rate for all polyps in back-to-back studies of colonoscopy is 21%, but the miss rate for non-adenomatous polyps is higher, reaching 27%. In Harrison and colleagues' study, the miss rate for hyperplastic polyps reached 59%.[32] High-quality bowel preparation, adequate luminal distension and an attitude particularly which is vigilant for flat lesions is mandatory to improve detection rate.

In this regard, advanced endoscopic techniques such as chromoendoscopy and NBI become significant (Figure 2). Chromoendoscopy significantly improves polyp detection, particularly of small proximal hyperplastic polyps. A summary of four randomised trials indicates that chromoendoscopy doubles the detection rate of hyperplastic polyps.[32] Moreover, a recently published randomised crossover study comparing high resolution endoscopy with NBI in SPS has demonstrated that polyp miss rate is higher in high resolution endoscopy (OR 0.21; 0.09-0.45).[33]

Besides, SSP are lesions difficult to resect endoscopically. In a recently published article that evaluated the rate of incompletely resected neoplastic polyps in clinical practice, two factors were independently associated: size and SSP. So, while incomplete resection rate was 7% in conventional adenomas, this rate reached 31% in SSP.[7] This is due to several reasons. Mainly, these lesions are flat or sessile, proximally located and it is difficult to determine the margins. To establish an optimal resection technique, efforts should focus on preparation for resection, the resection technique, and assessment of complete polyp removal. Especially, an increased attention to the polyp margin might improve outcomes. Outlining and marking the polyp margin before resection can enhance complete resection. Piecemeal resection should be avoided whenever possible. Endoscopic mucosal resection is safe and effective and is the method of choice. Use of targeted dye-spray or dye in the submucosal cushion to help define the lesion margin is helpful In some cases. Adjunctive ablation of the margins (argon plasma coagulation) after resection of large polyps can be useful to assure complete removal, and marginal biopsies after resection may be useful to increase confidence in the completeness of removal and aid in post-polypectomy management.[7, 30, 31, 34]

Surveillance Recommendations

In the recent years, several surveillance recommendations in SPS have been issued. However, all of these recommendations have a low level of evidence. Data on the risk of progression to CRC and on the risk to develop metachronic lessions are limited. So, the main reasons for more frequent colonoscopic surveillance are the increased rate of missed lesions and incomplete resection rate.[7, 30] East *et al*. made the following recommendations (grade D, level V): for patients diagnosed as having SPS, colonoscopy with pancolonic dye-spray is recommended every 1 to 2 years with resection of all lesions larger than 5 mm if possible. This resection is best performed at a tertiary centre with a special interest in the condition.[30] On the other hand, US Multi-Society Task Force on Colorectal Cancer recommends a one year interval after complete endoscopic resection.[30] Finally, if colonoscopy does not allow the total control of colonic polyps, colectomy with ileorectal anastomosis should be indicated (Table 1).[31] Based on the available recommendations, patients fulfilling the WHO criteria for SPS should be followed-up yearly with colonoscopy. However, there are patients with multiple serrated polyps not fulfilling the WHO criteria for SPS. In this situation, surveillance recommendations should be individualised taking into account number, location, histology and

familial history. Molecular markers can also play a role in the identification of these patients as high-risk.[35]

Conclusions

Endoscopic surveillance and CRC precursor lesions resection can reduce CRC incidence and surgery in AAP. Advanced imaging techniques should be used to reduce miss rates and to improve the definition of colonic lesions before endoscopic resection. Start time and frequency of endoscopic surveillance should be based on the risk of detecting a CRC, the progression period from adenoma or serrated lesions to CRC, the miss rate and the incomplete resection rate.

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How Should Early Neoplasia be Detected in Barrett's Esophagus? Take your Time at the Z Line and Use Dye!

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Introduction

Diagnosing early neoplastic changes in Barrett's esophagus is still a challenge for any endoscopist. Intraepithelial neoplasia usually only becomes evident in the form of minimal irregularities that lie level with the mucosa. Only careful observation of the Z line can lead to a diagnosis being established. It is not surprising that early carcinomas are often overlooked during routine endoscopy and that in the majority of cases esophageal carcinomas are only diagnosed at advanced stages. By contrast, early diagnosis not only allows curative treatment options but also maintains the patient's quality of life, with preservation of the esophagus.[1,2]

Large meta-analyses published in 2008 and 2010 and including 47 and 51 studies, respectively, calculated the risk of malignant degeneration in Barrett's esophagus as 5.3–6.5 cases per 1000 patient-years.[3,4] More recent studies have put much smaller figures on the rate of carcinoma development: a meta-analysis in the United States published in 2012 reported a pooled annual incidence for the neoplasia rate of 0.33%.[5] A study published in Denmark in 2011 also reports figures consistent with these new data.[6] The authors analysed data from a national pathology and cancer registry for a period of 17 years. A total of 11,028 patients with Barrett's esophagus were included, for whom data for a median of 5.2 years were available. A similarly low incidence of 1.2 adenocarcinomas per 1000 patient-years was also calculated.

This low incidence led the Danish authors to question the value of the surveillance programmes for patients with Barrett's esophagus that for decades have been recommended by the international specialist societies. Against the background of the limited prognosis for patients with advanced esophageal carcinoma and the higher incidence previously assumed, endoscopic surveillance for patients with Barrett's esophagus has been a firm component of the various guidelines published by international specialist societies.[7,8]

Four-quadrant biopsy sampling every 1–2 cm over the entire Barrett's segment and biopsying of suspicious lesions, as described in what is known as the Seattle protocol published by Levin *et al.*, continues to the present day to be the gold standard for the diagnosis of early neoplastic changes.[9] This recommendation dating from 1993 has never been tested by any prospective randomised studies.

Quality of Endoscopic Images

Modern imaging technology has made dramatic progress since 1993, however. Whereas endoscopes at that time had a resolution of approximately 200,000 pixels, devices with more than 850,000 pixels are available today. This technological development has made it possible to carry out detailed examination of the surface structure of the mucosa. The improved image quality is undoubtedly the most important aspect of the improvement in the quality of diagnosis.

Inspection Time

In addition to the need for optimal technical conditions, the inspection time involved has also naturally been a major factor influencing the rate of detection of early neoplasias. For example, a study published last year investigated the connection between the amount of time needed to inspect the Barrett's segment and the neoplasia detection rate and found that there was a good correlation between them. According to the study, a detection time of 1 min per 1 cm length of Barrett's esophagus appears to be useful.[10] During the inspection, attention should also be given to areas in which early neoplasias appear statistically most often. According to our own group's results, they usually lie in the area from the 12-o'clock to the 3-o'clock position.[11] A study conducted in Australia on the same issue was published in 2012. In the 146 patients with short-segment Barrett's esophagus (SSBE) who were examined, 50% of the neoplasias were located between the 2-o'clock and 5-o'clock positions.[12] It is therefore

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Figure 1. Early Barrett's carcinoma (Typ I) with acetic acid spraying.

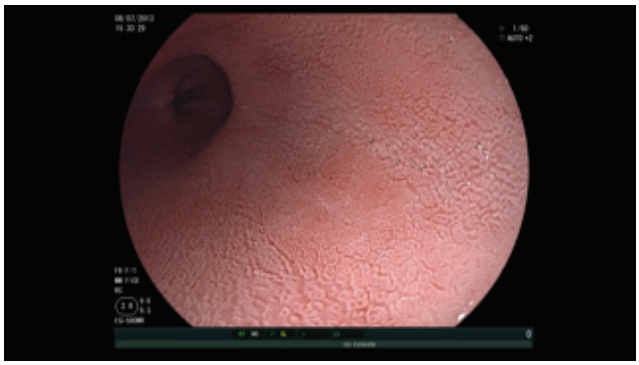

Figure 2. Early Barrett's carcinoma (Typ IIb) with acetic acid spraying.

certainly not a mistake to direct one's attention deliberately to the area between the 12-o'clock and 5-o'clock positions.

These simple measures — using high-resolution endoscopes and giving sufficient time to the inspection, focusing particularly on the typical early carcinoma locations between the 12-o'clock and 5-o'clock positions — can also be supplemented by chromoendoscopy.

Real Chromoendoscopy

The aim in chromoendoscopy is to visually emphasise any irregularities by enhancing the superficial mucosal structures (Figure 1, 2). The standard method that has become established for Barrett's esophagus is spraying of 1.5% acetic acid. After an application time of 1–2 minutes, this leads to an enhancement of the pit pattern. Mucosal irregularities and structural irregularities in the pit pattern are associated with the presence of early neoplasia. Two prospective studies have demonstrated a high degree of accuracy in the detection of early neoplasia in Barrett's esophagus using acetic acid spraying. A prospective study by our own group investigated the added value provided by four-quadrant biopsies in comparison with chromoendoscopy-guided targeted biopsies. In examinations conducted at a highly specialised endoscopy centre, the study found that the added value provided by four-quadrant biopsies was minimal.[13] Vázqez-Iglesias *et al*. also achieved excellent results in identifying early neoplasias in Barrett's esophagus using acetic acid spraying, with high levels of sensitivity and specificity.[14]

The state of the data on the advantages of methylene blue staining is heterogeneous, and in everyday practice the relatively large amount of time required for staining makes the procedure impracticable. Before methylene blue staining, the Barrett's segment has to be freed of mucus by applying acetylcysteine. After the methylene blue has been applied to the mucosa, it has to be left to take effect for 2 minutes. The method is therefore of value as a reserve technique in the hands of endoscopists familiar with it.

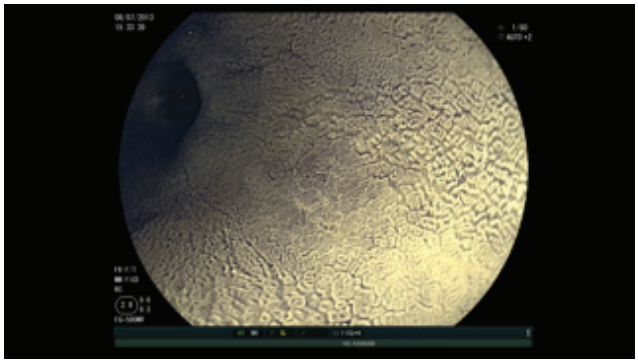

Figure 3. Early Barrett's carcinoma with computed virtual chromoendoscopy (CVC).

Virtual Chromoendoscopy

In contrast to real chromoendoscopy, virtual chromoendoscopy has the attractive feature that staining can be switched on by pressing a button (Figure 3). In addition, it is possible to switch back and forth several times from white light to staining. Three technologically different systems are available on the market — computed virtual chromoendoscopy (CVC), narrow-band imaging (NBI), and i-scan. Pohl *et al*. compared the sensitivity for detecting early neoplasias in Barrett's esophagus using real chromoendoscopy with acetic acid and virtual chromoendoscopy using the CVC system.[15] The method uses an electronic colour filter that enhances superficial and vascular structures. Real and virtual chromoendoscopy showed comparable results.

The great majority of publications have investigated the value of the narrow-band imaging (NBI) system, which uses an electronic light filter. In a group of patients with Barrett's esophagus with or without neoplasia, Wolfsen *et al*. showed that the detection rate for neoplasias and higher-grade neoplasias increases when the NBI system is used in addition to white light.[16] In a recent multicentre randomised study by Sharma *et al*., high-resolution white-light endoscopy was compared with NBI endoscopy.[17] Biopsy sampling following the Seattle protocol was carried out in the white light group, while in the NBI group biopsies were only taken from suspicious areas. The study included 123 patients. The analysis of the two groups showed comparable neoplasia detection rates, with a smaller number of biopsies in the NBI group.

These studies suggest that the detection rate for early neoplasia in Barrett's esophagus can be increased using chromoendoscopy. With the exception of the time required for the examination, there appear to be no differences between real and virtual chromoendoscopy in relation to the detection rate.

In the meantime, endoscopes have now become available with a high-resolution quality that include virtual chromoendoscopy (NBI) and an autofluorescence module; these are marketed using the term "trimodal imaging." In a prospective randomised crossover study including 99 patients with Barrett's esophagus, Curvers *et al*. showed that additional use of NBI and the autofluorescence system did not lead to any increase in the detection rate for early neoplasia in comparison with the use of high-resolution endoscopy alone.[18]

Endoscopic procedures that function at the microscopic level such as confocal endomicroscopy and endocytoscopy are not capable of gaining acceptance in practice. The large amount of time required and in particular the high degree of histopathological expertise needed by the endoscopist are not practicable in routine endoscopic work.

No validated biomarkers are available that are capable of predicting with a high level of sensitivity and specificity which Barrett's esophagus patients are at high risk for malignant degeneration. Various research groups such as the Barrett's Consortium in Germany are pursuing a very interesting approach at the genetic level. Genome-wide analysis is thought to be capable of identifying genes associated with a high risk for the development of Barrett's carcinoma. This could potentially allow the surveillance strategy to be individually adjusted depending on the patient's genetic background.

Even better than diagnosing early neoplasia in Barrett's esophagus would be an ability to prevent malignant degeneration. No preventive benefit has been demonstrated either for proton-pump inhibitor medication or for fundoplication surgery or weight reduction in obese patients. However, general measures such as avoiding nicotine or reducing obesity are basically useful.

A regular surveillance programme for early cancer recognition in patients with Barrett's esophagus is unquestionably essential. A high quality standard needs to be required here. To date, most esophageal adenocarcinomas have not been diagnosed in the setting of surveillance examinations — as the study in Denmark by Hvid-Jensen *et al*. mentioned above also reports. Two-thirds of the tumours were diagnosed at the index endoscopy or already in the first year after the diagnosis of Barrett's esophagus and were excluded from the study. Currently as yet unpublished data from our own group show that in Germany as well, only just under a quarter of early carcinomas are diagnosed during a surveillance examination.

These results are a reminder that index endoscopy examinations must be carried out with particular care. Using high-resolution endoscopy, allowing sufficient examination time (1 cm/min), giving special attention to the region between the 12-o'clock and 5-o'clock positions, and using chromoendoscopy — whether real or virtual — are particularly important.

Early diagnosis is undoubtedly of decisive importance for patients in relation to curative treatment options and maintenance of quality of life through the safe administration of local endoscopic therapy.

In brief: take your time at the Z line and use dye!

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P53 Immunohistochemistry in Patients with Barrett's Esophagus

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Introduction

Barrett's esophagus (BE) is a premalignant condition in which the squamous epithelium of the distal esophagus is replaced by columnar epithelium containing goblet cells.[1] BE patients have an increased risk of developing esophageal adenocarcinoma with an estimated incidence rate of 0.1-0.5% per year.[2-4] The development of esophageal adenocarcinoma is a gradual process in which BE epithelium, under the influence of acid exposure, evolves to low-grade dysplasia, high-grade dysplasia and eventually esophageal adenocarcinoma.[5, 6] Since early identification and treatment of dysplasia may prevent progression to esophageal adenocarcinoma, endoscopic surveillance is recommended to patients with Barrett's esophagus.[7] However, the value of surveillance is under discussion given the overall low incidence of neoplastic progression, large screening population, and lack of discriminative tests for risk stratification.[8-9]

Histology

Histological diagnosis of dysplasia is the only accepted predictor for neoplastic progression to date and is therefore used for defining surveillance intervals. International guidelines recommend surveillance every three years in patients with non-dysplastic BE, annual surveillance in patients with low-grade dysplasia and (endoscopic) treatment or surveillance every three months in patients with high-grade dysplasia.[7,10] However, histological diagnosis of dysplasia is subject to sample error and considerable interobserver variation, mainly because features of dysplasia may overlap with features of non-neoplastic regenerative changes, which limits its predictive value.[11] Although the predictive value of dysplasia increases with consensus of multiple pathologists, the annual incidence rate of low-grade dysplasia is still around 3-4%, while only 1-2% of these patients develop neoplastic progression in the following year.[12, 13] Thus, although low-grade dysplasia is associated with an increased risk of developing high-grade dysplasia or esophageal adenocarcinoma, the absolute risk of neoplastic progression remains low.

P53 Immunohistochemistry

Use of biomarkers in addition to histology may improve risk stratification and therefore the cost-effectiveness of BE surveillance. Aberrant p53 expression, defined as overexpression or loss of P53 as detected by immunohistochemistry appears to be one of the most promising biomarkers. Moreover, the immunohistochemical staining technique is widely established and available in most if not all pathology labs. The antibodies used for p53 immunohistochemistry not only detect protein derived from mutant TP53 but also from wild-type p53. Overall, p53 expression pattern is considered to be indicative for the presence of mutant TP53, because the latter has a longer half-life than wild-type p53 and is not degraded in the normal way. This results in accumulation of p53 in the cell nucleus, which is easily and reliable detectable by immunohistochemistry. One exception is the complete loss of p53 protein, possibly due to truncating mutations or loss of the gene, and therefore a negative p53 immunohistochemistry. Alternatively, epigenetic silencing may also result in absence of protein and thereby a negative immunohistochemical staining.[14] Although less common, loss of p53 expression is easy to identify because it sharply contrasts with the surrounding tissue (Figure 1). Initially, studies have focused on the value of p53 overexpression for predicting neoplastic progression in BE. However, recent studies have shown that loss of p53 expression may be even more important.[14, 15]

Identification of Dysplasia

The occurrence of p53 overexpression increases along the metaplasia-dysplasia-adenocarcinoma sequence. P53 overexpression is detected in 0-10% of patients with non-dysplastic BE, 10-50% of patients with low-grade dysplasia and even 60-100% of patients with high-grade dysplasia or esophageal adenocarcinoma (Table 1). Loss of p53 expression is especially seen in patients with high-grade dysplasia or esophageal adenocarcinoma.[12, 15-18] Aberrant pattern of p53 expression is detected more frequently in patients with low-grade dysplasia and neoplastic progression during follow-up than in patients

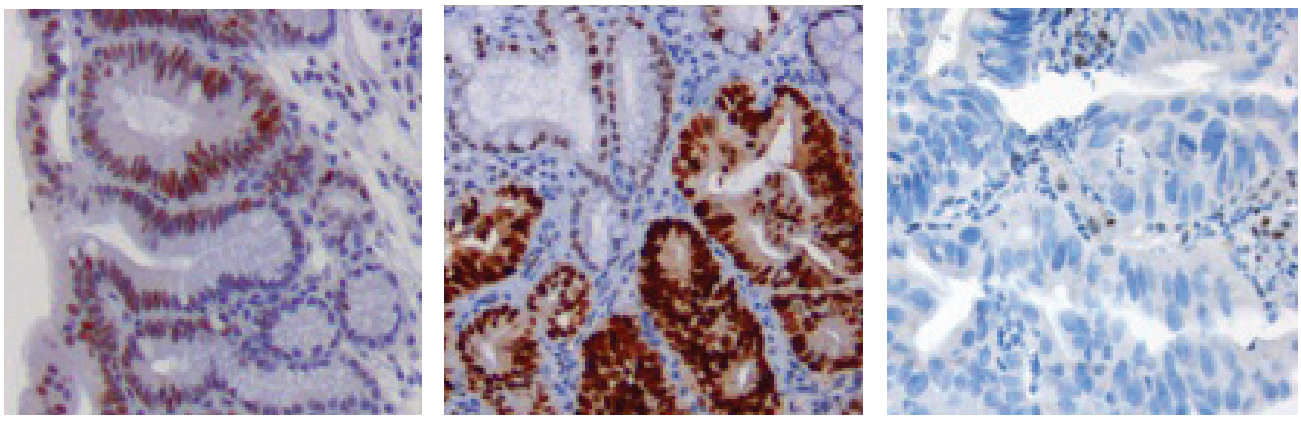

Figure 1. Barrett's esophagus with normal p53 expression (left), p53 overexpression (middle) and loss of p53 expression (right).

without progression, suggesting that p53 immunohistochemistry may help to distinguish true dysplasia from regenerative changes. Aberrant p53 expression may also be detected in patients with non-dysplastic BE and neoplastic progression during follow-up and may thus precede neoplastic development.[19] Aberrant p53 expression may be detected up to 5-years before the diagnosis of high-grade dysplasia or esophageal adenocarcinoma.[15]

Predicting Neoplastic Progression

P53 overexpression appears to be associated with a 5 to 6-fold increased risk of developing high-grade dysplasia or esophageal adenocarcinoma independent of histological diagnosis and with an annual incidence rate around 7-8%.[15, 16, 18] Most recently, it was discovered that not only p53 overexpression is associated with neoplastic progression, but that the risk may be even higher with loss of p53 expression.[15] Patients with both aberrant p53 expression and low-grade dysplasia appear to have an 12-fold increased risk of neoplastic progression with an annual incidence around 11%. The sensitivity of p53 immunohistochemistry for predicting progression is estimated to be around 50%, with a specificity of 85%.[15]

Interobserver Variation

Interobserver variation is a major problem in diagnosing dysplasia especially for low-grade dysplasia, which also limits its predictive value.[11] However, interobserver agreement for p53 immunohistochemistry is good. In approximately 90% of patients multiple pathologists agree on p53 protein expression by immunohistochemistry, which indicates that p53 is not only a theoretical but also a clinically suitable marker to predict neoplastic progression in BE patients.[15, 18] In addition, previous studies have shown that application of p53 immunohistochemistry improves interobserver agreement for histological diagnosis.[12]

Conclusion

P53 overexpression as well as loss of p53 expression is associated with an increased risk of neoplastic progression in BE patients. Immunohistochemical evaluation of the p53 protein status is a reliable method in daily practice. Although routine p53 immunohistochemistry is associated with higher costs than histological assessment alone, application of this marker may lead to the identification of a much smaller high-risk group needing intensive surveillance, thereby increasing cost-effectiveness of BE surveillance.

Author	Year	Study design	Sample size		Aberrant P53 immunohistochemistry					Predictive value (95% CI)	Interobserver variation
						ND	LGD	HGD	EAC		
Kastelein[15]	2012	Case-control	49 586	HGD, EAC ND, LGD	↑↓ ↑ ↓	11% 10% 1%	38% 33% 5%	83% 70% 13%	100% 57% 43%	RR 6.4 (3.6-11.3) RR 5.6 (3.1-10.3) RR 14.0 (5.3-37.2)	K 0.79
Sikkema[16]	2009	Case-control	27 27	HGD, EAC ND, LGD	↑ ↑↑	3% 0%		54% 40%		HR 5.4 (2.0-14.5) HR 1.8 (0.6-5.2	-
Kaye[12]	2009	Case-control	143 32	LGD, HGD, EAC ND	↑ ↓	0%	6%	58%	64%	-	-
Dekken[17]	2008	Cohort	88		↑ ↑↑	0% 0%	11% 0%	80% 70%	76% 64%	-	-
Murray[18]	2006	Case-control	35 163	HGD, EAC ND, LGD	↑ ↑↑	48% 11%		62% 32%		OR 6.3 (2.1-19.1) OR 8.4 (2.4-30.0)	K 0.86

Table 1. Studies evaluating the value of p53 immunohistochemistry in Barrett's esophagus. ND = non-dysplastic Barrett; LGD = low-grade dysplasia; HGD = high-grade dysplasia; EAC = esophageal adenocarcinoma; CI = confidence interval; RR = relative risk; HR = hazard ratio; OR = odds ratio.

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Symptoms Associated to Weakly Acidic Reflux and Esophageal Motility Abnormalities are more Common than Functional Chest-pain in Patients with Non-cardiac Chest Pain Refractory to PPI Therapy

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Introduction

Non-cardiac chest pain (NCCP) or unexplained chest pain, defined as recurring angina-like retrosternal chest pain of non-cardiac origin, is a highly prevalent disorder that affects up to 23% of the general population.[1] Patients with NCCP for which no cardiac aetiology is demonstrable are often evaluated for an esophageal aetiology. However, the pathophysiology of chronic NCCP remains to be fully elucidated. Identified underlying mechanisms are diverse and it is not uncommon to find overlap. Of the gastrointestinal causes, GERD is by far the most common cause of NCCP. Other gastrointestinal-related etiologic factors that have been proposed include esophageal motility disorders, abnormal mechanophysical properties of the esophagus such as sustained esophageal longitudinal muscle contractions, visceral hypersensitivity, altered central processing of intraesophageal stimuli, autonomic dysregulation and psychological comorbidity.[1,2] In particular, past studies have consistently demonstrated alteration in pain perception regardless of the presence of esophageal motility disorders in patients with NCCP.[2-4]

The diagnostic tests available to investigate the esophageal origin of NCCP include gastroscopy, esophageal manometry, ambulatory 24-hour esophageal pH monitoring and an empirical trial with high-dose proton pump inhibitor (PPI).[1,2,5,6] Upper endoscopy has a very limited value in NCCP patients, because of the low prevalence of esophageal mucosal findings.[7,8] Indeed, several studies have documented that about 65-70% of GERD population have no evidences of esophageal mucosal injuries and this percentage markedly increases depending on whether upper endoscopy is performed on-PPI therapy.[9-13] Ambulatory pH monitoring is particularly helpful in those patients who had normal endoscopy and failed to respond to a therapeutic trial with PPI.[14] Nevertheless, an empirical trial with PPI is considered the most effective test to diagnose NCCP and, eventually, to treat this disorder.[5,6,14] However, previous studies showed that PPIs are less effective in relieving NCCP than heartburn. In particular, a recent meta-analysis showed that the co-existence of objective measures of GERD, specifically a positive pH-monitoring study or reflux esophagitis, was strongly predictive of a positive response to PPI therapy, whereas the absence of such evidence was predictive of a poor treatment response.[15] Few data are available to explain the potential causes of this finding.

The aim of this study was to assess the frequency of esophageal motility abnormalities and reflux disease, assessed by the state-of-the-art method to investigate GERD that is impedance-pH monitoring,[16] in a large series of NCCP refractory patients.

Material and Methods

We evaluated consecutive NCCP patients presenting to the motility centres of eleven Gastroenterology Units in Italy, using traditional manometry and impedance-pH monitoring. Forty-eight healthy volunteers served as controls. They referred to our units to undergo upper endoscopy or pre-operative surgical evaluation, or to be studied because of PPI refractoriness. Inclusion criteria were: age >18 years; patients complaining of NCCP since at least 6 months with more than 3

Parameters	Refractory NCCP Patients	Healthy Volunteers
Patients, (n)	150	48
Female/Male (patients, n)	83F/67M	27F/21M
Mean Age, yrs (range)	48 (12-75)	44 (22-77)
Mean BMI, Kg/m2 (range)	25 (17-40)	23 (16-34)
Coffee consumption, n (%)	93 (62%)	36 (75%)
Smoking, n (%)	35 (23%)	14 (29%)
Alcohol Drinking, n (%)	57 (38%)	22 (46%)
Patients with Hiatal Hernia, n (%)	62 (41%)	15 (31%)
Endoscopic Assessment		
Endoscopy negative, n (%)	141 (94%)	48 (100%)
Erosive esophagitis, n (%)	9 (6%)	0 (0%)
Barrett's esophagus, n (%)	0 (0%)	0 (0%)

Table 1. Demographic and clinical characteristics of 150 PPI-refractory NCCP patients and 48 healthy volunteers.

episodes per week; patients non-responders to double-dose PPI therapy (symptom relief < 50%). Exclusion criteria were: patients with history of thoracic or digestive surgery; patients with primary or secondary severe esophageal motility disorders (i.e. achalasia, scleroderma); patients with a positive cardiologic work-up explaining the chest pain. Patients who underwent the impedance-pH testing off-therapy were asked not to take PPIs for at least 20 days before the motility testing. During the washout period, patients were permitted to use an antacid.[17]

The study protocol was approved by the local Ethics Committees and performed according to the Declaration of Helsinki. All patients gave written informed consent before the start of the study.

All subjects who agreed to participate in our study underwent an upper endoscopy and, subsequently, conventional esophageal manometry with 24-hour impedance-pH monitoring within 1-5 days from endoscopic examination. Endoscopic assessment was evaluated according to international criteria.[18, 19] Manometric pattern was defined according to published criteria as follows: Normal peristalsis (NP; normal wave amplitude and progression), Ineffective Esophageal Motility (IEM; lower distal wave amplitude in ≥30% of wet swallows), Distal Esophageal Spasm (DES; simultaneous wave progression in >10% of wet swallows with normal/high distal amplitude), Nutcracker Esophagus (NE; normal wave progression and high distal wave amplitude).[20, 21] During 24-h impedance-pH all patients underwent a scheduled Mediterranean diet (total calories intake 2300Kcal/day).[22] Then, we measured for each patient esophageal acid exposure time (AET), total number of reflux episodes (acid/weakly acidic) and symptom-reflux association using both symptom association probability (SAP+ if ≥95%) and symptom index (SI+ if ≥50%). An impedance-pH test was considered positive or GERD in case of abnormal AET (% time pH<4 more than 4.2%) and normal AET but positive symptom-reflux association, as previously reported.[23] Patients with normal AET and negative symptom-reflux association were considered as affected by functional chest-pain (FCP).

Statistical analysis was performed by means of the non-parametric Wilcoxon signed rank test because experimental data were not normally distributed. The results were considered statistical significant when p value was less than 0.05.

Results

Detailed demographic and clinical characteristics of our patients are reported in Table 1. One-hundred and fifty (83F/67M; mean age 48, range 12-75) consecutive NCCP patients, non-responders to PPI therapy and reporting at least one symptom during the monitoring day, were enrolled. Their demographic and clinical data did not differ from the demographic and clinical characteristics of healthy individuals: 27 females; median age 44 years (range 22-77 years); BMI 23 kg/m^2 (range 16 – 34 kg/m2) (p=ns).

The examinations were well tolerated by all subjects and no important technical failure occurred.

Manometric Data

At manometry testing, 96 (64%) patients had NP, 35 (23%) had DES, 16 (11%) had NE and 3 (2%) had IEM (i.e. 54 (36%) had motor abnormalities) as shown in Figure 1. Overall, patients with NCCP had more frequently esophageal motility abnormalities than healthy volunteers (p<0.05).

Impedance-pH Data

At impedance-pH monitoring, 50 patients were studied on- and 100 off-PPI treatment. As illustrated in Figure 2, we found 26 (17%) patients with an abnormal AET, although 5 (4%) of them were on-PPI therapy (i.e. acid GERD). Out of the remaining 124 (83%) patients with normal AET, 16 (11%) had a positive SAP/SI to acid reflux (i.e. hypersensitive esophagus to acid), 39 (26%) to weakly acidic reflux (i.e. hypersensitive esophagus to weakly acidic or weakly acidic GERD) and 14 (9%) to both

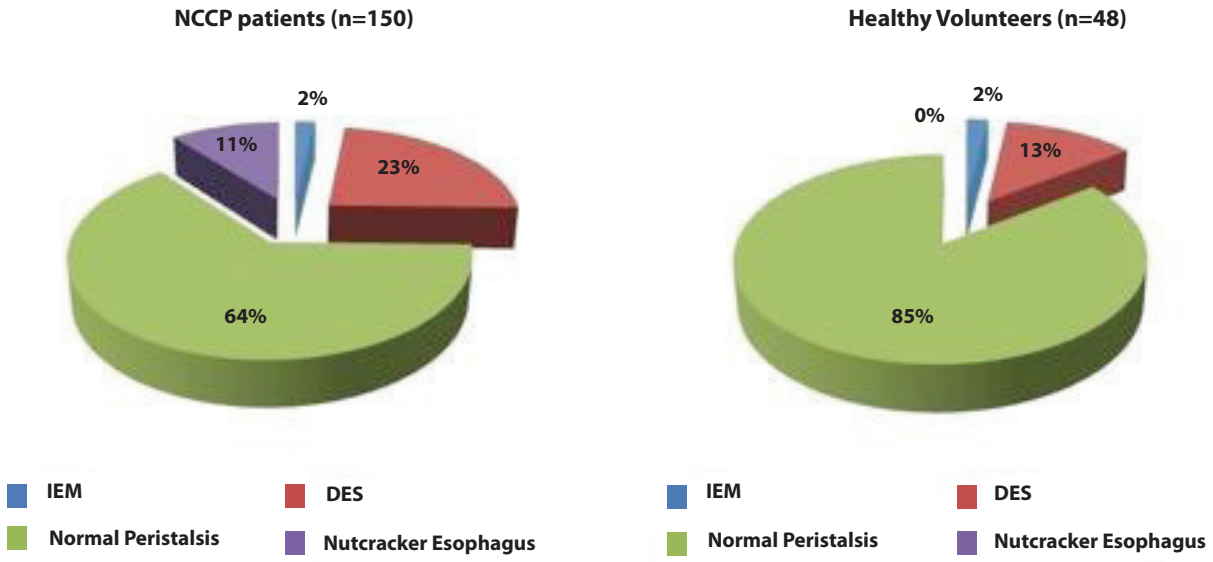

Figure 1. Esophageal motility abnormalities identified by means of conventional manometry in 150 PPI-refractory NCCP patients and in 48 healthy volunteers.

acid and weakly acidic reflux (i.e. mixed GERD). Fifty-five (37%) patients had no association between reflux and symptoms and, out of them, 34 (23%) had NP (i.e. functional chest-pain patients).

Discussion

Non-cardiac chest pain is considered to be central chest pain that resembles angina yet, after appropriate investigation, its cause appears unrelated to the heart. This condition is a common presenting complaint in primary and secondary care, affecting up to 23% of the general population.[1] After exclusion of cardiac ischaemia, strong evidence supports an empirical trial of high-dose acid suppression to evaluate and to treat GERD. However, different studies highlighted that patients with NCCP tend to respond less to PPI therapy than those with typical reflux symptoms (i.e. heartburn and regurgitation) and a recent systematic review by Kahrilas *et al*. showed that the absence of co-existence of objective measures of GERD, specifically a positive pH-monitoring study or reflux esophagitis, is strongly predictive of a poor response to PPI therapy.[15] Therefore, patients with negative endoscopy and normal acid exposure are more likely to have a negative response to acid suppression therapy and, from a diagnostic point of view, a negative PPI test that may erroneously lead to exclude GERD as the main cause of NCCP. In addition, very limited data are

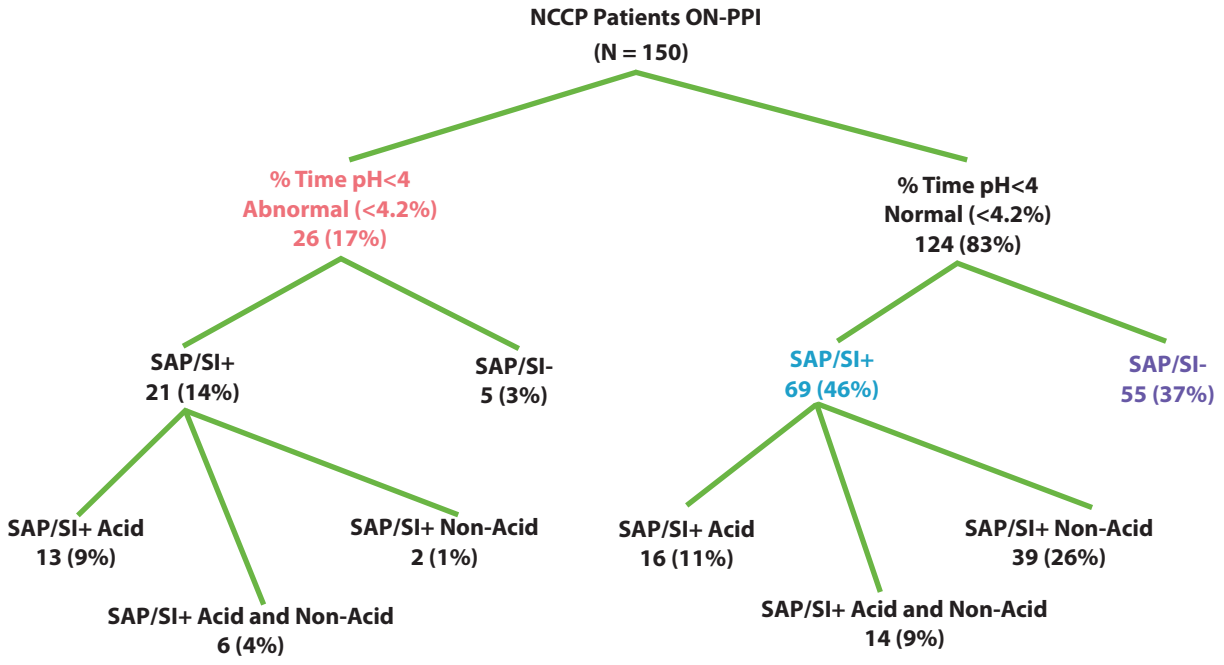

Figure 2. Impedance-pH findings identified by 24-hour impedance-pH monitoring in 150 PPI-refractory NCCP patients.

available on the real-life frequency of functional chest-pain in this population since very few investigations assessed concomitantly the presence of esophageal motility abnormalities and pH-metry profiles in the same series of NCCP subjects and, more importantly, there are no studies evaluating these findings by means of impedance-pH monitoring, the current state-of-the art method to diagnose GERD. Recent investigations underlined the major role of this novel diagnostic technique in clinical practice, since one of its major advantages is the ability to detect both acid and weakly acidic reflux, and so far to correlate symptoms reported during the monitoring day to both kind of refluxes.[16, 24] This allows us to exclude with a very good accuracy GERD as the major cause of symptoms.

In the present study, we found that 26% of patients with NCCP who did not respond to PPI therapy had symptoms associated to weakly acidic reflux and, additionally, 14% of NCCP patients had symptoms which correlated to both acid and weakly acidic reflux. These results underscore the major role of weakly acidic reflux in refractory NCCP patients, quantifying the diagnostic yield of impedance-pH reflux monitoring compared with pH-only reflux monitoring. In fact, the subgroup of NCCP patients with normal esophageal acid exposure and positive temporal association between symptoms and weakly acidic reflux episodes is larger than the subgroup of NCCP patients with normal esophageal acid exposure and positive temporal association between symptoms and acid reflux events. These interesting results may be partially explained by the visceral hypersensitivity as well as alterations in pain perception that have been demonstrated in patients suffering of NCCP.[1-4] Indeed, it is reasonable to hypothesise that in this kind of patients, symptoms may develop in case of stimulation of esophageal chemoreceptors by acidic refluxate and, also, in case of stimulation of mechanoreceptors by weakly acidic refluxate after the distension of the esophageal wall where the mechanoreceptors are located.[3-4]

Furthermore, these results are novel as they reveal the proportion of NCCP patients with a positive symptom association for weakly acidic reflux as it helps in narrowing down the proportion of patients otherwise being labeled as presenting with "functional chest-pain". The practical impact of this subcategorisation is that these patients might benefit, in addition to the acid-suppressive therapy, from a reflux-reducing therapy. Recent evidence, although uncontrolled, suggests that patients with symptomatic non-acid reflux episodes can be successfully treated with a surgical therapy.[24-27] Additionally, preliminary data reveal that drugs aimed at reducing visceral hypersensitivity should be adopted in patients with hypersensitive esophagus (such as antidepressant agents and selective serotonin reuptake inhibitors). Unfortunately, few placebo-controlled trials aimed at demonstrating the effectiveness of such compounds in the relief of symptoms of these hypersensitive patients have been performed, but a study by Greek authors has demonstrated that citalopram, a selective serotonin reuptake inhibitor, is better than placebo in controlling heartburn in patients with hypersensitive esophagus.[28]

Finally, it is relevant to underline that the combined use of conventional manometry and impedance-pH monitoring allowed us to identify an esophageal aetiology for NCCP experienced by our patients non-responding to PPI therapy in about 77% of the cases, whereas no motor abnormalities or absence of GERD were observed only in a minority of them (23% of patients were considered as affected by functional chest-pain). Thus, this combined approach, mainly thanks to the application of impedance-pH testing, permitted us to markedly increase our diagnostic yield in this type of patients and to reduce the need for additional investigations aimed at understanding other causes of NCCP. On the other hand, as the main limitation of this study, we have to acknowledged that the clinical significance of our findings in terms of therapeutic outcome has to be investigated, and further studies are necessary to elucidate the real impact of this novel diagnostic approach.

Conclusions

Symptoms related to weakly acidic reflux and esophageal motility abnormalities are very common in NCCP patients non-responding to PPI therapy and may be responsible for their persistence in the majority of these patients. Our data support the use of manometry and ambulatory impedance-pH monitoring in a diagnostic algorithm for NCCP patients refractory to PPI therapy, in order to identify a cause and, potentially, to treat it. Moreover, this approach permits to identify NCCP patients affected by functional esophageal chest-pain and suggests to consider other potential aetiologies of the disorder.

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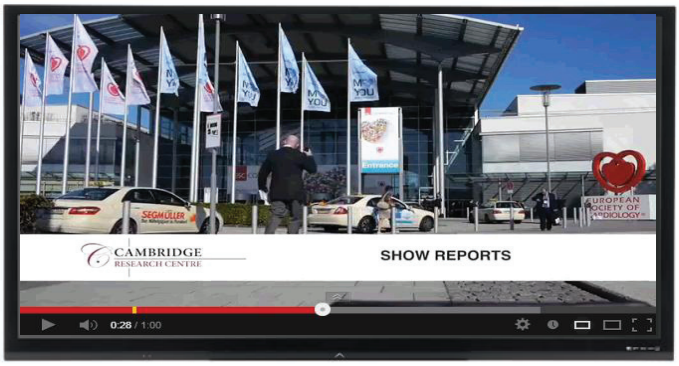

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Is there Still a Need for a New Strategy in Helicobacter pylori Eradication?

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Helicobacter pylori (*H. pylori*) is one of the most prevalent pathogens, as more than 50% of the world population is colonised by this micro-organism. The main risk factors are low socio-economic level and bad hygienic conditions. In consequence, the prevalence of *H. pylori* infection is lower and begins later in developed countries where 30-40% of the population is infected in adulthood, while in developing countries this rate reaches 80-90% in adulthood and most children are already colonised by 10 years of age.[1]

Gastroduodenal symptoms and pathologies develop in 10-15% of the infected population with *H. pylori* being well-recognied as one of the aetiological agents of peptic ulcer and a risk factor for the development of gastric adenocarcinoma and lymphoma.[2]

The treatment currently available for colonised symptomatic patients includes a combination of antibiotics (amoxicillin, clarithromycin, metronidazol, etc.) and a proton-pump inhibitor (omeprazol, lanzoprazol, pantoprazol, etc.) or bismuth for 1-2 weeks. As experience in treating the infection was gained, these drugs have been used in different combinations and developed regimens have been tailored in various parameters (dosage, dosing intervals, duration of treatment) in order to provide the best outcome in terms of efficacy and tolerability. However, despite the continuous efforts made by the gastroenterologists, the optimal empirical treatment remains to be discovered as the available treatment nowadays does not eradicate *H. pylori* in all patients, because of the appearance of antibiotic resistance and a moderate patient compliance due to adverse effects such as vomiting, diarrhoea, abdominal pain and taste alterations. Therefore, the treatment of *H. pylori* infection has become a common problem in many practice settings.[3]

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Authorities have proposed that infection with *H. pylori* should be approached and treated as any other bacterial infectious disease. This implicates, as a general rule, that clinicians should prescribe therapeutic regimens that have a per protocol (PP) eradication rate of at least 90% (grade B level) and probably at least 95% (grade A level), in keeping with the existing practice in the field of other common bacterial infectious diseases.[4]

Even with the current most effective treatment regimens, ≥20% of patients will fail to eradicate *H. pylori* infection. Therefore a variety of regimens have been tested in patients with persistent *H. pylori* infection. The most commonly used salvage regimen is a bismuth-based quadruple therapy. Also several antibiotics have been used in salvage regimens including levofloxacin, rifabutin, and furazolidone. Given the potential benefits of sequential therapy in patients with clarithromycin-resistant *H. pylori* infection, one wonders about its use in patients with persistent infection. It also remains unclear how failure of bismuth-based quadruple or sequential therapy should be managed. One potential disadvantage of these therapies is that patients with failed eradication would have limited options for further treatment, because they would already have received 3 different antibiotics: amoxicillin, clarithromycin, and nitroimidazole.[5]

Perhaps the 2 most recognised important predictors for treatment failure nowadays include, as mentioned before, patients non-compliance and resistance of *H. pylori* to specific antibiotics. The significant negative impact of clarithromycin resistance on the efficacy of clarithromycin-containing triple therapy has been discussed many times. Nevertheless, if culture is not performed after failure of PPI-clarithromycin-metronidazole, and hence antibiotic susceptibility is unknown, several "rescue" options may be suggested. Metronidazole resistance is more prevalent than clarithromycin resistance; however, its clinical impact can be minimised by the use of higher doses or the inclusion of a PPI in quadruple regimens. From a practical standpoint, clinicians should adhere to several general recommendations when

they are faced with a patient who has persistent *H. pylori* infection despite a previous course of antimicrobial therapy. Under no circumstances should the same antibiotic regimen be used. Certainly, if clarithromycin was used in the initial treatment, it should be avoided in any salvage regimen. It also is advisable to offer salvage regimens for a duration of 10 to 14 days.[6]

Compliance with therapy is the perhaps the most important factor in H. pylori eradication. Compliance with *H. pylori* eradication regimens is truly a multifactorial process. Current evidence and published guidelines recommend complex and prolonged eradication regimens, using a number of antibiotics and involving manipulation of gastric pH as well. This complexity provides challenges for both the physician and the patient. For the physician, it demands a clear understanding of the pathogenesis, sequelae and complications of *H. pylori* infection and a motivation to test for and treat the infection where appropriate. The motivated physician can then provide information to the patient which will lead to his or her empowerment to play an active role in their treatment by complying with therapy. Compliance with therapy has a considerable influence on treatment failures in antibiotic-sensitive patients and in the subsequent development of antibiotic resistance. This has major implications. It has been proven that 10% of patients prescribed *H. pylori* eradication therapy will fail to take even 60% of medications. It has also been proven that progressively poorer levels of compliance with therapy are associated with significantly lower levels of eradication. The importance of structured aftercare and follow-up of patients is also of critical significance. Compliance with *H. pylori* eradication regimens is a multifactorial process.[7,8]

The use of probiotics and foodstuffs with bioactive components in *H. pylori*-colonised subjects with gastric inflammation is supported by many observations. Specific strains of *Lactobacillus* and *Bifidobacterium* exert *in vitro* bactericidal effects against *H. pylori* through the release of bacteriocins or production of organic acids, and/or inhibit its adhesion to epithelial cells. Such protective effects have been confirmed in animal models. Some clinical trials have evaluated the effect of probiotics in colonised adults and children and have shown that the administration of probiotics improves *H. pylori* gastritis and diminishes *H. pylori* density. This effect is statistically significant, but weak. On the other hand, any study could demonstrate the effect on eradication of *H. pylori* infection by probiotic treatment. These results indicate that probiotics generally do not eradicate *H. pylori*, but due to the mentioned decrease of the density of colonisation maintain lower levels of this pathogen in the stomach. In association with antibiotic treatments, some probiotics increase eradication rates and/or decrease adverse effects due to the antibiotics. On the other hand, the antioxidant and anti-inflammatory properties exerted by probiotics may stabilise the gastric barrier function and decrease the mucosal inflammation. Considering that the risk-benefit ratio is positive because of their favourable safety profiles, the final decision to add a probiotic to eradication therapy should weigh the clinical trial results against patient-specific aspects. It has previously been suggested that the usefulness of probiotic adjunct therapy is particularly relevant in patients with a history of gastrointestinal intolerance to antibiotic treatment. Other factors to take into account should include patient preference and the probability that supplementation in capsule form could lead to decreased compliance due to the greater number of daily pills to ingest, or to a cumbersome treatment protocol that is incompatible with the patient's lifestyle. The additional cost to therapy should also be discussed with the patient and analysed against the loss of productivity or of work hours because of treatment-associated side-effects, most notably diarrhoea and epigastric discomfort.[9]

As mentioned above, *H. pylori* eradication often fails due to antibiotic resistance or adverse effects of therapy. *Lactobacillus* spp. exhibit anti-*H. pylori* activity *in vitro*, inhibiting *H. pylori* urease activity and adhesion, secreting short-chain fatty acids, bacteriocins/bacteriocin-like substances and acting as immunomodulators. Adding probiotics to regimens reduces side-effects by 11-23% and may slightly improve eradication rates by ≤ 5-15%. Although it is controversial whether the probiotics reduce development of antibiotic resistance in the intestinal microflora, it was shown that ingestion of probiotics (*L. acidophilus* and *Bifidobacterium*) was found to reduce the emergence of resistant enterococci. Activity of the lactobacilli is species and strain specific. Probiotic mixtures should be considered carefully as the proinflammatory activity of one probiotic can mask the anti-inflammatory effect of the others. Another treatment adjunct is *S. boulardii*, which is immunomodulatory and inhibits bacterial adhesion and toxins. Briefly, probiotics reduce the side-effects of *H. pylori* regimens and may slightly increase eradication success.[10]

Conclusion

There is no doubt, that *H. pylori* is the major pathogen for gastroduodenal diseases worldwide and causes a high morbidity and mortality. The development of an effective antibiotic treatment has remarkably changed the management of peptic ulcer disease and other *H. pylori*-related diseases. Current first-line treatment regimens are effective and safe, but over the past decade they are declining in efficacy, mainly because of an increasing antibiotic resistance. Therefore, the cure of *H. pylori* in clinical practice is becoming progressively more difficult and one can ask the question of whether there is still a need for a new strategy in eradication of *H. pylori*. Novel therapeutic strategies have provided promising results and new developments are ongoing. Research efforts should also continue to be focused on the development of simple, safe, tolerable and efficacious treatments. The identification of alternative therapeutic strategies to overcome these limitations is a pressing issue. Although altering the duration of treatment or the choice of first-line antibiotics can target resistance patterns, lack of

adherence to treatment because of adverse events has been addressed mostly through the addition of probiotics to eradication regimens, in an attempt to re-establish the gastrointestinal microbial equilibrium. Regardless of their mechanism of action, probiotics may provide a novel approach to the management of *H. pylori* infection. The risk of developing *H. pylori*-associated diseases may increase with an increasing level of *H. pylori* density. Numerous animal and human studies have demonstrated a decrease in *H. pylori* density and inflammation following the intake of probiotics. On the other hand it is known from other areas that small changes in disturbed functions have major clinical effects. In any equilibrium between aggression and defense, minor changes are sufficient to prevent or precipitate disease. Therefore, it can be suggested that the weak but persistent effect of lactobacilli on *H. pylori* gastritis could prevent diseases such as gastric cancer or peptic ulcer. This hypothesis should of course be evaluated in the future by well-designed large studies and there is still a lot of work to be done in order for all the other novel regimens to be sufficiently validated and therefore possibly recommended as first-choice therapies ushering in a new era of anti-*H. pylori* treatment.

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How to Optimise the Prevention of HBV Vertical Transmission?

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Introduction

Hepatitis B virus (HBV) infection is one of the most common viral infection in the world, with more than 350 million chronically infected people.[1] This burden is responsible for about 1 millions deaths per year, largely linked to hepatocellular carcinoma (HCC),[1] despite the availability of an extremely effective vaccine for over 25 years.[2] This is closely due to insufficient public health policies in high endemic areas (Asia and Africa) where more than 8% of the population is chronically infected, and where the implementation of an efficient preventive strategy is difficult. The persistence of chronic infection in these areas is largely due to vertical (mother-to-child) transmission.

Vertical HBV Transmission

In high endemic regions, most infections occur at birth or at a very young age. These infections remain asymptomatic and the risk of chronic evolution is very high. In South-East Asia, in the East or in Pacific regions, 30 – 50% of chronic infections are of vertical origin linked to a high viral load in mothers.[1, 3, 4] In Africa, South-America and in the Middle East, where viral loads seem to be less, vertical transmission represents only 10 – 20% of chronic infections.[1, 3, 4]

Vertical HBV transmission occurs essentially during delivery. In mothers with high HBV replication rate detected by hybridisation (equivalent cut-off at 700,000 copies/mL), the risk of vertical transmission is about 90% in the absence of prophylaxis and the risk of chronicity for the newborn is about 80 – 90%.[5, 6] Maternal infection by a pre-C mutant (HBeAg negative mothers), which is associated with a lower viral load than the wild-type virus (HBeAg positive mothers), reduces the risk of transmission and of chronic infection in the newborn. In absence of detectable maternal HBV-DNA, the risk of infection is between 10 – 30% depending on the cut-off level of HBV-DNA testing.[5, 6]

Usually, vertical transmission is due to chronic maternal infection. However, if an acute HBV infection occurs in the 3rd trimester of pregnancy, the active viral replication at time of delivery explains that it is transmitted in 65 – 100% of cases.[7, 8] Due to the long incubation time of HBV (6 weeks to 6 months), acute hepatitis in the post-partum period can also cause infection, which is likely attributable to the maternal viral load at time of delivery in absence of any clinical manifestations.

Recommendations for Vaccination and Sero-vaccination

World Health Organization (WHO) recommended that routine infant immunisation programmes were implemented in all countries.[9] Furthermore, in high endemic countries, WHO recommended that the first dose of hepatitis B vaccine was given as soon as possible and in practice before 24 hours of life, corresponding to a birth-dose vaccine without testing the HBsAg status in mothers.[9] In 2006, 163 of 193 WHO members (84%) have introduced hepatitis B vaccination in their national infant immunisation programme and 81(42%) birth-dose vaccine.[10] For the sub-group of high endemic countries, the implementation rates were 84% and 44%, respectively.[10] However, the implementation of a birth-dose vaccine could be

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challenged in resource-limiting countries for economical and logistical reasons, especially for home deliveries.[11]

In developed countries, like US or Western Europe where Hepatitis B Immune Globulin (HBIG) are disposable, it is usually recommended to test the maternal HBsAg status and if the mother is HBsAg positive, to administrate sero-vaccination to the newborn in the first 12 hours of life, which consists of a first IM injection of HBV vaccine, and at another site, an IM injection of HBIG;[7] booster vaccine injections have to be done at 1 and 6 months for completing vaccination. The vaccination schedule of 0, 1 and 6 months with paediatric dose (10 µg) is usually used except in some countries for premature birth with a 0, 1, 2 and 12 months schedule. The dose of HBIG is usually 100 IU (or 30 IU/kg). In some countries also, in case of maternal HBeAg positivity (i.e. at risk of high viral load), a dose of 200 IU at birth, repeated at 1 month was proposed, sometimes associated with a double dose vaccination. Despite its frequent use, there is no clear demonstration of the superiority of this reinforced sero-vaccination schedule. In some developing countries, this strategy of screening and sero-vaccination is also possible despite economical and logistical limitations.[12, 13]

Effectiveness of Sero-vaccination

A lot of trials have compared vaccination alone, HBIG alone and sero-vaccination with different schedules with placebo or no intervention.[7] Briefly, vaccination alone or HBIG alone is better than placebo or no intervention, but sero-vaccination is better than vaccination alone or HBIG alone.[7] Lee *et al*. did not find any difference between doses, schedules, time of the first injection (< 12 hr, 12 to 24 hr or > 24 hr) and plasma derived or recombinant vaccine for the efficacy of prevention of vertical transmission.[7] However, a lack of power due to small number of newborns in sub-group analysis could be advocated. Furthermore, these trials usually did not stratify on the maternal viral load but only in some cases on the HBeAg status.

Sero-vaccination prevents mother-to-child vertical HBV transmission in 89 to 100% of cases: in 85-92% of newborns of mothers with active viral replication and in 100% of newborns of mothers with non-replicative HBV.[7, 8] Children will develop an adequate anti-HBs response (which is supposed to be evaluated within the first year of life) with a protective titer over 10 mIU/mL in 80% of cases. Then, antibody concentrations decrease over time in such a way that around 80% of these children will maintain effective protection 5-14 years later. Recently, a large study performed in 640 children who completed sero-vaccination demonstrated the persistence of protective anti-HBs antibodies in 70, 40 and 25% of children at 5, 10 and 15 years of age.[14] The question of whether sero-vaccinated children should be called back for booster vaccination after the age of 15 years remains a matter of debate, but is not a recommendation.

Systematic sero-vaccination - or at least vaccination- of children born from HBV infected mothers, followed by of all children and adolescents then by universal vaccination, has been performed in Singapore, Taiwan and Alaska: such a policy yielded a major reduction in the rate of HBsAg carriage, a significant reduction in acute and chronic hepatitis B and in liver-related mortality, mostly by reduction of HCC rate both in adults and in children.[15-17] The neonatal HBV vaccination was the first to demonstrate that a vaccine was able to dramatically reduce the risk of cancer.

Sero-vaccination Failures

Sero-vaccination is a very potent but not totally efficient method to prevent vertical HBV transmission. Failure to sero-vaccination could be related to the lack of adherence to recommendations which is probably the main problem in western countries, and have to be regularly evaluated and corrected. Variations in the S gene have been also associated with vaccination failure, but probably plays a minor role in clinical practice.

Finally, *in utero* HBV transmission is probably the main cause of sero-vaccination failure especially in Asia. There is now great evidence in the literature that high maternal HBV DNA levels are associated with a risk of HBV vertical transmission despite a complete sero-vaccination.[18-21] This probably reflects an in utero transmission as suggested by the positivity of HBV markers in peripheral blood in infants at delivery.[18] Other factors, like HBeAg maternal status or mode of delivery, do not seem to be associated with *in utero* transmission when maternal HBV DNA is systematically measured. The highest HBV DNA levels are found in HBeAg positive pregnant women especially during the immune tolerance phase, and this could explain the role of maternal HBeAg status previously advocated in older studies.

If the correlation between maternal HBV DNA level and sero-vaccination failure[18-21] is clear, the cut-off "at risk" level is not clearly determined: sero-vaccination failure occurred at a level as low as 5 log IU/mL but the risk is significant only above 7 to 8 log IU/mL.[21]

Anti-HBV Analogues in Late Pregnancy to Reduce *in utero* HBV Transmission?

The proof of concept for a benefit of the administration of an anti-HBV analogue in late pregnancy associated with sero-vaccination on the risk of HBV vertical transmission is now clearly demonstrated. A recent meta-analysis, including 15 randomised control trials, demonstrated a clear benefit of the addition of lamivudine to sero-vaccination on both *in utero* HBV transmission, evaluated by HBsAg positivity (Relative Risk around 0.33 to 0.43) or HBV DNA positivity (Relative Risk around 0.33) at birth or at 6 to 12 months of life.[22] Moreover, this meta-analysis suggested that the benefit for late administration on lamivudine in pregnancy was only effective if the maternal viral load decreased under treatment below 6 log at delivery.[22] Similar results have been recently reported with Telbivudine and there is no benefit to introduce the pre-emptive treatment at the second instead of the third trimester of pregnancy.[23, 24] Finally, if the treatment was not

indicated for maternal liver disease, the anti-HBV analogue could be stopped between 1 to 3 months after delivery without significant increase in the risk of ALT flares.[25]

Among anti-HBV analogues, some safety data in human pregnancy were disposable only for lamivudine, telbivudine and tenofovir.[26] Telbivudine and tenofovir are listed by the FDA in the B category for pregnancy safety, although lamivudine is classified in C. Tenofovir and lamivudine have a long resume in pregnant women since more than a quarter of HIV positive pregnant women are currently on tenofovir-including regimen. Recent data suggested also that tenofovir, contrary to lamivudine or telbuvidine, could be administrated in case of breast-feeding since very few if any is excreted in human milk and absorbed by newborns.[27] Finally, tenofovir appears to be a good alternative since this drug demonstrated a high anti-HBV activity with no anti-HBV resistance to date. Even if the safety profile of these drugs is encouraging, more data have to be collected on long-term safety among children *in utero* exposed to these analogues.

Conclusions

Universal HBV vaccination strategies is effective and cost-saving in countries of intermediate or high endemicity, with less consistent benefit in countries of low endemicity. These efficient strategies are economically difficult in developing countries, but are frequently sub-optimal in developed nations in relation to the lack of systematic adherence to general recommendations. Specific strategies are also implemented in pregnant women. Systemic HBsAg detection during pregnancy followed by optimal sero-vaccination of newborns is a very efficient method to prevent HBV vertical transmission. However, it is insufficient in some cases, related to *in utero* HBV transmission associated with high maternal viral load (above 7 to 8 log IU/mL). In these particular cases, the role of anti-HBV analogues during the 3rd trimester of pregnancy, associated with sero-vaccination, as to be discussed to optimise the prevention of vertical transmission. This strategy could also decrease the need for reinforced sero-vaccination and for caesarian section, which is sometimes recommended in some countries in these cases.

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Molecular Escape Mechanisms from Treatment with NS3 Protease Inhibitors in Chronic Hepatitis C

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Introduction

Hepatitis C virus infection is an important cause for end-stage liver disease and hepatocellular carcinoma, with approximately 170 million people chronically infected worldwide.[1] Tremendous strides have been made in the development of effective antiviral drugs that can be administered orally to block viral replication, with the ultimate goal to eradicate the virus. The first two approved direct-acting antiviral agents (DAAs), telaprevir (Incivek®) and boceprevir (Victrelis®), both ketoamide inhibitors of the virus NS3 serine protease, are indicated for use in patients with genotype 1 HCV infection. They mark the beginning of an extraordinary new era in HCV therapy.[2] The high genetic diversity of HCV within infected persons, however, is a challenge for effective small molecule antiviral compounds, with clinical trials showing rapid selection of resistance-associated amino acid variants (RAVs), most of which are considered to pre-exist. Viral variant fitness and the degree of resistance are two major determinants driving their selection from within the viral quasispecies under drug pressure.

Resistance Development Against Ketoamide Protease Inhibitors

RNA viruses such as HCV generate a "cloud" of variant viruses within infected individuals. The so-called quasispecies population accumulates mutations over time due to nucleotide misincorporation by the viral NS5B polymerase and absence of proof-reading activity. Mathematical arguments suggest that every possible RAV is likely to pre-exist at a low frequency in the replicating viral quasispecies of the typical HCV-infected patient.[3] Given this genetic diversity, it is possible that naturally occurring polymorphisms in the NS3 sequence could provide a priori resistance to protease inhibitors, and thus negatively impact the success of future treatment regimens. Up to 5% of DAA-naïve patients show baseline NS3 protease RAVs,[2] however, early evidence suggests no significant impact on virus eradication as reported from triple regimens containing telaprevir (PROVE 1 and 2 trials[4, 5]) or boceprevir (SPRINT-2 trial[6]). Thus, baseline RAVs may be of limited clinical significance at present as they are likely suppressed by the peg-interferon/ribavirin backbone in current standard-of-care regimens. However, they can be expected to be of substantial importance to future interferon-sparing, all-oral combination therapies.[7, 8]

Natural variation in residues that neighbour ketoamide compounds in the ligand-binding site of the NS3 protease has recently been analysed in genotype 1a HCV.[9] Dominant strains were retrieved from DAA-naïve patients collected from geographically diverse sites, previously deposited in the public European HCV database[10] (http://euhcvdb.ibcp.fr/euHCVdb/). Such binding-site variants in NS3 at one or more ketoamide-neighbouring residues are found in approximately 7.8% of the genotype 1a sequences analysed in this study.[9] Overall, 13 different variants in the ligand-binding site have been identified (Figure 1), from which some amino acid changes (Q41H, T42A, T42S, V55I, I132V, K136R, F154Y, and T160A) have not been identified in previous *in vivo* or *in vitro* studies. Importantly, four of these dominant variants from DAA-naïve patients, Q41H, I132V, R155K, and D168G, cause low-to-moderate levels of ketoamide resistance in HCV cell culture, from which three are highly fit (Q41H, I132V, and R155K) (Figure 2).[9]

Although boceprevir and telaprevir are both linear ketoamide compounds, they show distinct structural features which contribute

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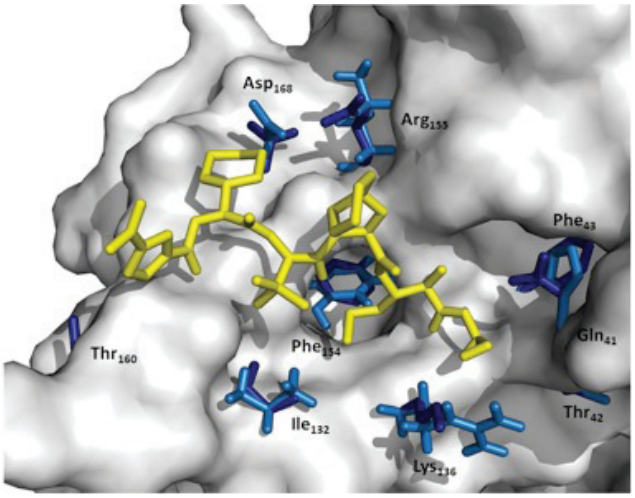

Figure 1. NS3 protease ligand-binding site variants. Surface representation of the natural substrate binding site of the NS3 protease with co-crystallised telaprevir-like ligand from Protein Databank structure 2P59 and binding-site variants identified in HCV genotype 1a dominant strains (adapted from Welsch *et al.*[9]).

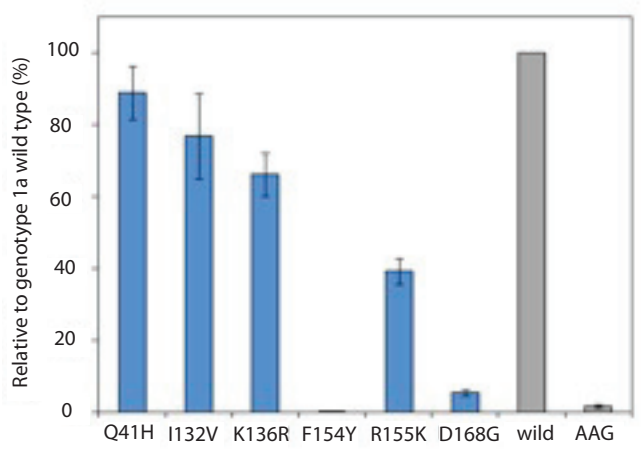

Figure 2. RNA replication fitness of NS3 protease binding-site variants. Replication capacity of NS3 protease ligand-binding site variants in H77S.3 cell culture (wild: wild type; AAG: negative control) (adapted from Welsch *et al.*[9]).

to different half maximal effective concentrations (EC50) against genotype 1a HCV in cell culture and could also pose a distinct risk for RAV selection among binding-site variants. Telaprevir possesses a different P4 capping group and a cyclopropyl group at P1′ that is not present in boceprevir. Furthermore, the P2 group is different in both compounds with a smaller isopropyl-proline in boceprevir than the cyclopental-proline in telaprevir (Figure 3). Based upon *in silico* structure modeling, two ketoamide-neighboring variants that were already previously identified in clinical settings, R155K and D168G, are likely to affect binding of telaprevir more than boceprevir. Measurements of antiviral susceptibility in cell culture studies are consistent with this observation. Here, R155K and D168G led to a 2- to 4-fold greater increase in the EC50 of telaprevir compared with boceprevir, and almost a 9-fold increase in the telaprevir EC50.[9]

Varient Fitness in Ketoamide Resistance

The quasispecies comprise genetically distinct but closely related viral genomes that are competing within a highly mutagenic environment. Typically the wild type as dominant strain is detectable along with minor strains that are present at much lower frequencies, depending largely on the viral fitness of the variant strains.[11, 12] The fitness of a virus can be defined as its "relative ability to produce infectious progeny".[11, 12] Variants that harbour resistance mutations are usually less fit in RNA replication and/or infectious virus production and thus present in much smaller quantities in the quasispecies population than the wild-type virus. The replication capacity is one measure of variant fitness which depends on proper processing of the viral polyprotein by the NS3 protease. Since ketoamide compounds are mimicking the natural substrate, they likely select for binding-site variants that interfere with their binding to the protease substrate-binding site. Conversely, they can also interfere with protease substrate recognition and cleavage. Thus, binding-site variants can be expected to negatively influence RNA replication due to altered recognition of the polyprotein substrate related to structural changes similar to those leading to ketoamide resistance. Besides RNA replication, the capacity to assemble infectious virus particles contributes to the fitness phenotype of a mutant virus. Although yields of infectious virus generally correlate well with the replication capacity, some NS3 protease mutants in a cell-culture model of HCV infection reproducibly demonstrated greater impairment in their ability to produce virus than predicted from reductions in their RNA replication capacity.[13] These particular mutations nestled together at one edge of the protease substrate-binding site, which abuts the helicase domain in a crystallographic structure of the full-length NS3 molecule. It is likely that these residues are involved in domain-domain interactions between protease and helicase required for virus assembly as they did not demonstrate defects in viral egress from infected cells and no significant difference in the specific infectivity of extracellular particles.[13] Although modest in magnitude, such defects might be exponentially magnified during the multiple cycles of cell infection occurring in an infected patient. Despite this, most of the resistant mutants with a specific drop in their infectious virus yield have been identified in patients previously enrolled in clinical trials of ketoamide compounds. A possible explanation for this observation is second-site mutations with compensatory mechanisms for protein structural changes.

Compensatory Mutations, Long-term Survival and Wild-type Reversal of Ketoamide Resistant Variants

RAVs could become fixed in the viral quasispecies population due to compensatory second-site mutations. As an example, the binding-site variant F154Y is found lethal for RNA replication when placed in the background of the genotype 1a HCV strain H77S.3 in cell culture (Figure 2).[9] The complete loss of RNA replication could be due to direct interaction/clash of the Tyr154 side-chain with the polyprotein substrate. The presence of Tyr154 in the public sequence database, however, suggests that the F154Y amino acid variant is capable of functioning in an alternative sequence context, as second-site substitutions in the same strain might compensate for fitness deficits.

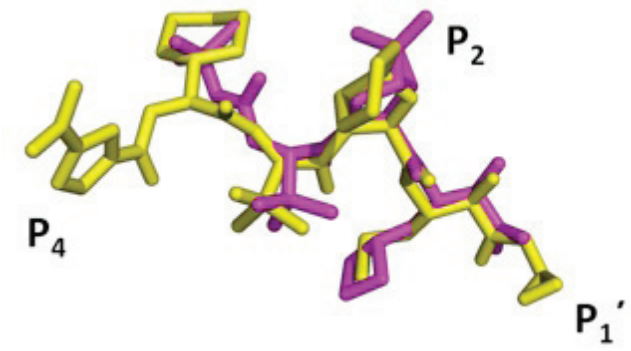

Figure 3. Scaffold of ketoamide NS3 protease inhibitors. Ketoamides boceprevir (magenta) and telaprevir-like ligand (yellow) with distinct chemical structural differences at P4, P2 and P1' (adapted from Welsch *et al.*[9]).

In fact, the respective sequence from the European HCV database containing the F154Y substitution showed two additional substitutions in NS3 that differ from the genotype 1a consensus sequence.[9] The emergence of such compensatory mutations capable of rescuing impaired replication capacity offers the potential to escape from drug pressure under DAA therapy. Their selection may allow resistant strains at a low but evolutionarily neutral and highly connected region in the overall fitness landscape to outcompete other viral variants that are located at a higher but narrower fitness peak in which the surrounding mutants are less fit. Another example is the NS3 protease RAV V55A, which has recently been identified by clonal sequencing in a long-term follow-up study in genotype 1 HCV patients who previously received telaprevir or boceprevir as monotherapy.[14] One patient showed V55A as dominant strain already at baseline, and this was still detectable at long-term follow-up. This observation is unexpected, taken into account the compromised variant fitness of this variant virus with RNA replication of only 28% compared to wild type and a distinct drop in infectious virus yield leading to a relative infectivity of only 3.1% compared to the wild-type virus (Figure 4).[15] The steep decline in infectious virus yield is particularly surprising given the fact that the V55A variant is found repeatedly in public databases. Accordingly, second-site changes may explain how this variant could become fixed in the viral quasispecies and even dominate in some treatment-naïve and -experienced patients.

Given the results from clinical trials with regimens combining multiple classes of DAAs, there is still potential to achieve viral cure even in patients who fail on a protease inhibitor-based triple therapy.[2] Without compensation for fitness deficits, RAVs that emerge during therapy clear over time, allowing the wild-type virus to re-establish and dominate. However, the appropriate waiting time before potential protease inhibitor re-exposure is unknown.

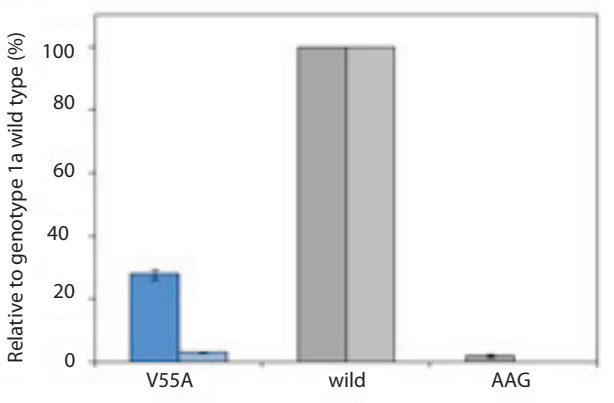

Figure 4. RNA replication and infectious virus yield of the ketoamide resistant V55A variant. Replication capacity (left) and infectious virus yield (right) of the V55A NS3 protease RAV in H77S.3 cell culture (wild: wild type; AAG: negative control) (adapted from Welsch *et al.*[15]).

Conclusions and Future Perspectives

Viral fitness coupled with the degree of resistance conferred by resistant variants is likely to be the major determinant driving selection of variants from within the viral quasispecies during therapy. Most resistant variants show distinct fitness deficits from either impaired RNA replication and/or reduced infectious virus yield. However, second-site changes may explain why some resistant variants persist upon treatment discontinuation while others do not, and how resistance-associated variants that negatively impact virus replication could dominate in some treatment-naïve patients. Such naturally existing variants are found in dominant virus strains before DAA exposure. They are of substantial relevance to the success of DAA-containing regimens, but may be of limited clinical significance at present as they are likely to be suppressed by peg-interferon/ribavirin. These variants might also affect future generations of inhibitors depending upon their chemical structures. Thus knowledge on the natural variability in structures targeted by antivirals can help guide the development of future generation DAAs. The peg-interferon/ribavirin backbone in the current standard of care needs to be replaced for future all-oral regimens by another backbone with a low chance of resistance development.

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Conflict of Interest

The author has no conflict of interest to declare.

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Management of Irritable Bowel Syndrome

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Introduction

Irritable bowel syndrome (IBS) is a functional bowel disorder characterised by symptoms of abdominal pain or discomfort associated with disturbed defecation and often accompanied by bloating and/or distension.[1] The syndrome is viewed as a defined aggregation of common symptoms rather than as a single disease entity; these symptoms may reflect disturbances in any one or a combination of a number of physiological processes.[2] The purpose of this review is to provide an overview on the current understanding of the pathophysiology of IBS and its impact on current treatment options, as well as guiding future possibilities of management

Epidemiology

IBS accounts for 10-15% of primary care visits and 25-50% of referrals to a gastroenterologist.[3] In the general population, using the Rome III definition, the prevalence of IBS is around 10% in most Western populations.[4] In general, IBS is twice as common in females than males[3-5] and seems to decline in prevalence with advancing age.[5]

Pathophysiology

In considering symptomatic therapies in IBS it has proven useful to consider three general mechanisms that are thought to generate symptoms in IBS:

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1. Altered gut reactivity (motility, secretion) in response to luminal (meals, gut distention, inflammatory mediators, bacterial factors) or provocative environmental stimuli (psychological stress) resulting in symptoms of diarrhoea/constipation.
2. A hypersensitive gut with enhanced visceral perception resulting in pain.
3. Dysregulation along the brain-gut axis.[2]

Altered Gut Reactivity

In IBS, diarrhoea can be seen to occur as a result of a number of colonic sensori-motor mechanisms including high-amplitude propagated contractions (HAPCs), an enhanced gastrocolic response and rectal hypersensitivity.[6-8] The latter may be an important contributor to urgency, which is such a troubling symptoms for many IBS sufferers. Constipation may, in turn, be secondary to increased segmental (non-propulsive) contractions, decreased HAPCs, or reduced rectal sensation.[9-11] Abdominal pain may also be associated with HAPCs.[12] Other parts of the gastrointestinal tract may also be involved. For example, a greater increase in phasic contractions in the terminal ileum and colon has been observed following luminal distention, eating fatty meals and the administration cholecystokinin in IBS in comparison to control subjects.[13] Colonic motility is augmented in IBS by food, stress, anger, or the instillation of the deconjugated bile acid, deoxycholic acid; while these responses are not specific for IBS, they do seems to be accentuated in subjects affected by this disorder.[14] Taken together, these abnormal or accentuated motor responses led to the assumption that dysmotility was a primary abnormality in IBS and to anti-spasmodics becoming a widely employed therapy.

Visceral Hypersensitivity

Since the 1970s multiple studies have confirmed that balloon distention in the rectum induces pain at lower volumes in patients with IBS.[15] These observations led to the concept of visceral hypersensitivity as a fundamental factor in IBS. Several neurotransmitters and/or neuromodulators may be relevant to hypersensitivity, including serotonin (5-hydroxytryptamine; 5-HT),

neurokinins and calcitonin gene-related peptide (CGRP).[16] The capsaicin receptor on nerve fibres, also called the transient receptor potential vanilloid-1 (TRPV1) may also mediate pain in the rectosigmoid colon in IBS;[17] the N-methyl-D-Aspartate receptor (NMDA) that modulates central neuronal excitability has also been proposed as relevant to pain transmission in IBS.[18] Alternately, serine proteases, derived from either mast cells or the microbiota have been shown to damage tight junctions and increase intestinal permeability via proteinase activated receptors (PARs); these effects could, in turn, facilitate access for luminal triggers to sub-mucosal sensory neurons.[19]

Dysregulation Along the Brain-gut Axis

The concept of a bidirectional line of communication between the brain and the "little brain", the gut, is central to our current understanding of IBS. Clinically, the impact of the brain-gut axis is seen in the precipitation of symptoms by stress in so many IBS subjects. Other manifestations include autonomic dysfunction, hyper-responsiveness of the hypothalamic-pituitary-adrenal (HPA) axis, aberrant central representation and perception of visceral events and, even, cognitive deficits.[20] Into this milieu comes another important factor in IBS: psychological co-morbidity. While IBS should not be regarded as a psychological disorder, co-morbid anxiety or depression will exacerbate symptoms and impair the sufferer's quality of life.

Other Factors

Abdominal distention and bloating are frequent and distressful symptoms in IBS, although the etiology of these symptoms is unclear. Though bacterial fermentation has been linked to flatulence and changes in the microbiota have been described in IBS, the contribution of the microbiota to these or other symptoms in IBS is unclear. Both small Intestinal bacterial overgrowth (SIBO) and quantitative and qualitative changes in the faecal microbiota have been linked to IBS; the status of SIBO remains controversial,[21, 22] and findings in relation to the microbiota require confirmation in larger patient populations.[23]

Even though the normal intestine is perennially in a state of constant inflammation, inflammatory cells including mast cells[24-27] and activated T lymphocytes[28, 29] are increased above this "normal" level in the mucosa in a subset of patients with IBS. Prior exposure to bacterial pathogens (post-infectious irritable bowel syndrome, PI-IBS), changes in the microbiota, exposure to deconjugated bile acids or food antigens could all be contributors to this pro-inflammatory state. Mast cells release tryptase and histamine and have been observed to lie in close proximity to colonic sensory nerves in patients with IBS; their proximity has been correlated with abdominal pain.[30]

Colonic inflammation is associated with the production of serotonin, prostaglandins, bradykinins, adenosine, and nerve growth factors.[31] Because of its important roles in gut motility and sensation, abnormal release of 5-HT might have a central role in various manifestations of IBS[32] by initiating or suppressing the peristaltic reflex through increased availability of 5-HT (diarrhoea) and/or desensitisation of 5-HT receptors (constipation).[33]

In summary, there is no shortage of potential targets for therapeutic interventions in IBS. It remains unclear as to how many of these are epiphenomena; this may explain why so many attempts to base new therapies on a proposed pathophysiological mechanism, be it motility or visceral sensation, have proven disappointing. Another problem with many therapies directed at the neuromuscular apparatus of the gastrointestinal tract has been their non-specificity, resulting in adverse events in other organs such as the bladder and the heart. Similarly, the primacy of more recently described phenomena in IBS, such as an altered microbiota or low-grade inflammation, has yet to be defined.

Treatment Strategies in IBS

Two basic approaches may be taken to the management of IBS, symptomatic or disease-modifying. As success with the latter approach has proven largely elusive, the focus, for the most part, has been on individual symptoms.

When undertaking any treatment strategy in IBS consideration must be given, not just to predominant symptom(s), but also to the severity of these symptoms, their effect on the sufferer's quality of life, as well as the presence of co-morbidities, such as anxiety, depression or other psychosocial difficulties. Sufferers with mild symptoms often self-manage by instituting dietary and life-style changes and using over-the-counter medications for relief of symptoms; should they seek medical care, such patients usually respond well to education on the nature and natural history of the disorder, reassurance that it is not a life-threatening condition and usually do well and symptomatic remedies.

Symptomatic Management

A primary goal of symptomatic therapy has been to address what is perceived as the sufferer's predominant symptom(s). While extrapolation from research on constipation and diarrhoea, *per se*, has led to the development of a number of agents for the management of constipation-predominant (C-IBS) and diarrhoea-predominant (D-IBS) IBS, efforts to address pain, bloating and distension, often the most distressing symptoms for the sufferer, have been less successful and the management of these symptoms is often empirical.

Abdominal Pain

Antispasmodic medications have traditionally been used to reduce the basal and postprandial hyper-contractility seen in the colon in patients with IBS.[2, 34-36] While some anti-spasmodics, such as hyoscine, cimetropium, pinaverium and peppermint oil may provide some relief, their benefits tend to be transient and there is little evidence for

long-term effects in IBS.[35] The role of dietary fibre in pain management is unclear;[36] when shown to be beneficial, effects have been marginal and, in some instances, insoluble fibre has actually had a negative effect.[36]

Antidepressants have been found to be useful in the management of IBS-related abdominal pain.[37] Both tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) have been employed. The former have anticholinergic effects which, on the one hand, may reduce colonic "spasm" but, on the other hand, may lead to unwanted side-effects such as dry mouth and somnolence. While the precise mechanism of action of anti-depressants in IBS remains unclear, these drugs may alter central pain perception, especially in relation to stress, at doses that are considerably lower than those that achieve their antidepressant or anxiolytic effect. TCAs should be reserved for patients with frequent or severe pain.[2, 34, 35] Even though most trials have seen no benefit for SSRIs in terms of effects on bowel dysfunction or pain, patients have reported global benefits, particularly related to somatisation.[34, 37]

Constipation

Dietary fibre (≥ 25 g/day) has been traditionally recommended for patients with constipation-predominant IBS (C-IBS).[2] Fibre supplementation increases fecal mass and may accelerate transit.[38] Fruits and vegetables contain both soluble (pectins, hemicellulose) and insoluble (cellulose, lignin) fibre, while cereals and bran contain mainly insoluble fibre. Although the usual recommendation is to increase dietary fibre, particularly cereal bran, in C-IBS, this makes the symptoms worse in 55% while only 11% report benefit.[36] Soluble fibre may be better tolerated and fibre supplements such psyllium and ipsaghula, which are not only soluble but poorly fermented, may be especially suitable.[2] The main drawbacks to the use of fibre are flatulence and bloating.[35, 36]

Inorganic salts such as magnesium and polyethylene glycol (PEG) are effective and well-tolerated in chronic constipation,[38] though there is little data to recommend their use in IBS-C.[34-36] The osmotic laxative PEG will increase bowel movement frequency, but has had no impact on pain.[35] Organic alcohols and sugars, such as lactulose, which are also effective in chronic constipation, may promote flatulence and bloating, diminishing their tolerance in IBS.[34] Stimulant laxatives have not been studied in C-IBS and given their unpredictability in terms of effect and their association with tolerance cannot be recommended for use in IBS.[34]

Lubiprostone is a CI-2 Chloride Channel activator that has been approved by the Food and Drug Administration (FDA) for the management of both chronic constipation and IBS-C.[39, 40] Lubiprostone promotes a chloride and fluid secretion which lubricates the stool and, thereby, promotes spontaneous bowel movements. Lubiprostone's primary effects are in increasing the frequency of bowel movements and improving stool consistency. Side-effects have included nausea, abdominal pain and diarrhoea.[41] It should not be used in patients with bowel obstruction or pre-existing diarrhoea.[39-41]

Linaclotide, a minimally absorbed, 14-amino acid peptide agonist of guanylate cyclase-C, has shown benefit in the treatment of IBS-C.[42-44] Linaclotide increases intracellular cyclic guanosine monophosphate (cGMP), triggering a signal transduction cascade that results in the activation of the cystic fibrosis transmembrane conductance regulator. This activation causes secretion of chloride and bicarbonate into the intestinal lumen resulting in an increase in fluid secretion and acceleration of colonic transit. Compared to placebo, linaclotide has been shown to improve frequency of spontaneous bowel movements, complete spontaneous bowel movements, discomfort, and bloating, as well as global measures, in IBS-C.[42-44] Both laboratory studies and clinical observations suggest that linaclotide may have a specific effect on pain mediated by a GMP-related modulation of sensory afferents, suggesting that this class may have more global benefits in IBS-C.[42] Another GC-C agonist, plecanatide, is currently in development.

An alternative approach to constipation is to stimulate motility. Tegaserod is a 5-HT4 receptor agonist that was studied in high-quality randomised controlled trials where it demonstrated improvements in global symptoms of IBS-C (discomfort, bloating, and bowel movement frequency).[45, 46] Tegaserod was linked to a small number of cardiovascular (myocardial infarction, unstable angina) and cerebrovascular (stroke and transient ischemic attacks) events and was, therefore, withdrawn from the market in the US and elsewhere in 2007.[35]

While novel and more selective prokinetics, such as prucalopride and velusetrag have been developed for constipation and other indications, neither has been evaluated, to date, in IBS-C.[47]

Diarrhoea

The opioid analogs loperamide and diphenoxylate stimulate inhibitory presynaptic receptors in the enteric nervous system leading to inhibition of peristalsis and secretion. Loperamide reduces stool frequency and soiling and improves stool consistency in IBS but has little or no effect on abdominal pain.[35] Loperamide is preferred to diphenoxylate-atropine because it causes neither confusion nor anticholinergic side-effects.[35] It can be used either on a regular basis, as needed or in anticipation of events that have, in the past, precipitated diarrhoea. Loperamide has the added advantage of being available in syrup form so that the dose can be titrated to minimise constipation. Tolerance does not seem to occur with chronic dosing.

Cholestyramine, the bile acid binding agent, can be considered for patients with diarrhoea related to cholecystectomy or in instances of suspected idiopathic bile acid malabsorption.[2]

Alosetron is a 5-HT3 receptor antagonist that was evaluated in high-quality clinical trials, and showed superiority in subjects with

D-IBS over placebo in treating abdominal pain, urgency, global IBS symptoms and diarrhoea.[48, 49] However, alosetron was associated with an increased incidence of severe complicated constipation, as well as ischemic colitis. Rates of 1.1 cases of ischemic colitis and 0.66 cases of complicated constipation per 1000 patients-years were reported in relation to alosetron use.[50] Despite their rarity, the severity of these complications led to the use of alosetron being tightly regulated in the US by a prescribing program set up by the Food and Drug Administration (FDA).

Bloating

The management of bloating continues to represent a major challenge. As bloating is usually associated with constipation, it may be relieved by treatments that relieve this symptom, such laxatives. However, there is little evidence to support this approach. Others have recommended a primarily dietary approach, such as reducing dietary fibre and, particularly wheat bran, in non-constipated IBS. Indeed, more recent data, has suggested that a gluten-free diet may have more global benefits in IBS.[51] Bloating, without measurable evidence of abdominal distention, may be related to altered gas transit[52] and/or visceral hypersensitivity; the latter might benefit from TCAs but has not been formally tested.

Another novel dietary approach, also based on reducing fermentable substances in the diet has been the low- fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) diet. Though this diet is complex and rather restrictive, it has led to improvement in individual as well as global symptoms in IBS.[53]

Initial studies reported that more than three quarters of all IBS sufferers had a positive lactulose breath hydrogen test, suggesting the presence of small intestinal bacterial overgrowth.[54] This observation provided a rationale for assessing antibiotics in IBS. Rifaximin is a non-absorbable antibiotic that has demonstrated efficacy in three randomised clinical trials evaluating patients with D-IBS.[55-57] It demonstrated small but statistically significant improvements, over placebo, in global IBS symptoms, as well as in bloating. It is important to note that tests for SIBO were not performed in these pivotal trials leaving the mechanism of action of rifaximin, in IBS, unclear.[55-57] Given the recurrent or chronic symptom pattern that characterises IBS, and the theoretical risk of any long-term antibiotic, a recommendation for chronic or intermittent use of rifaximin cannot be made at this time. Furthermore, rifaximin is not, as yet, FDA-approved for the treatment of IBS.

Probiotics and prebiotics represent another approach to modifying the gut microbiota in IBS[58] and, indeed, some probiotics have been shown to benefit bloating and, in some specific instances, to have more global effects,[59] in IBS. The interpretation of probiotic studies in IBS remains challenging as studies have employed different species, strains, preparations and doses in various patient populations and often in sub-standard trials. When critically analysed, while lactobacilli appeared to have no impact on symptoms, probiotic combinations and bifidobacteria do seem to improve symptoms in IBS with some bifidobacterial strains providing more global relief.[60]

Novel Approaches

Crofelmer is a chloride fluid transport receptor inhibitor that inhibits apical transport of chloride and fluid, as well as providing anti-inflammatory and analgesic effects, which was assessed in a phase 2b trial for diarrhoea predominant IBS (IBS-D) but did not produce any significant benefits on bowel function.[61]

Arverapamil is r-isomer of the calcium channel blocker verapamil, which is selective for intestinal calcium channels and relaxes gut smooth muscle. Initial studies in IBS showed promise.[62]

A motilin receptor ligand agonist, mitemcinal, is being studied for IBS-C due to its effects as a prokinetic.[63]

The μ-opioid antagonist methylnaltrexone has been approved by the FDA for opioid-induced constipation[64] and could have some role in the management of IBS-C by modulating visceral sensation in peripheral visceral afferent nerves.

In the hypothalamic-pituitary-adrenal axis the hormone that primarily orchestrates the stress response is corticotropin-releasing hormone (CRH). Give the frequency with which IBS subjects report symptoms as being stress-related, a non-selective CRH antagonist was studied in a small cohort of IBS patients and resulted in decreased levels of anxiety, as well as beneficially modulating sensation and motility.[65]

Given that autonomic dysfunction has been described among IBS subjects both α-2 receptor agonists, as well as a β-3 receptor agonist,[66] have been developed for IBS; to date, there are insufficient data to allow one to assess the potential of these agents in IBS.

The non-sedating compound, dextofisopam, binds to 2, 3 benzodiazepine receptors in the subcortical and hypothalamic regions of the brain. Such receptors have modulatory effects on such autonomically-influenced gastrointestinal functions as sensation and motility. In initial studies, dextofisapam was well-tolerated and provided relief of overall IBS symptoms as well as reducing stool frequency and improving stool consistency.[67]

Conclusion

Many factors are involved in the development and exacerbation of symptoms in IBS; though many promising advances have been made in the field and a number of hypotheses advanced, the primacy of any one of these many factors in IBS pathophysiology remains to be defined. As a consequence, developing drugs targeted at a specific mechanism continues to represent a high-risk

approach. For this reason, as well as concerns regarding potential adverse events, drug development in IBS continues to be symptom-focused; thus, the attractiveness of "simpler" approaches such as dietary modification and the use of probiotics. Meanwhile, though representing intriguing targets, the roles of inflammation, as well as the gut microbiota, in IBS need to be better defined before therapeutic interventions such as antibiotics and anti-inflammatory drugs can be recommended.

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Chronic Pancreatitis and Pancreatic Insufficiency in Chronic Alcoholic Liver Disease

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Introduction

Chronic alcohol consumption is a major cause of morbi-mortality all around the world. Alcohol affects every organ and causes a variety of disorders. Liver damage ranges from liver steatosis to cirrhosis. Although the most common cause of chronic pancreatitis has always been alcohol, others factors have also been studied, such as smoking. It is unknown how many years of alcohol intake are needed to produce pancreatic damage, but it is estimated to be less than that required to produce liver damage.

Most epidemiological studies conducted between 1960 and 2000 pointed to alcohol as the main cause of this disease, reporting that habitual consumers of alcohol accounted for 70% to 80% of patients.[1-6] More recently, doubts have been cast on the role of alcohol as a cause of chronic pancreatitis, with some studies reporting it to be responsible for only 34% to 44% of cases.[7-9] Controversy also exists regarding the association between duration of alcohol intake and the development of chronic pancreatitis and liver disease.[10-12]

Chronic Pancreatitis and Pancreatic Insufficiency

Chronic pancreatitis is characterised by progressive damage that may impair the endocrine and exocrine functions of the gland; this damage is associated with the progressive development of both ductal and parenchymal histopathological and morphological changes in the exocrine and endocrine functions.[13]

There are no clearly defined laboratory parameters for the diagnosis of chronic pancreatitis. Some patients present with non-specific abdominal pain as the only manifestation. At advanced stages, patients may experience exocrine insufficiency and diarrhoea or changes in bowel habits with or without weight loss. In these cases, diagnosis can be made either by directly quantifying the pancreatic enzymes in the duodenal juice after hormonal intake or stimulation, or by measuring the substrates produced by inadequate pancreatic enzyme digestion. In the most severe cases, endocrine failure is manifested as diabetes mellitus.

The morphological diagnosis of chronic pancreatitis requires images — whether simple abdominal X-rays, abdominal ultrasound, computed tomography, magnetic resonance or endoscopic retrograde cholangiopancreatography. As the most sensitive diagnostic method, endoscopic ultrasonography is the diagnostic tool of choice.[14] To test for exocrine pancreatic insufficiency, the breath test is gradually replacing tests like faecal elastase measurement, given its easy implementation and high diagnostic sensitivity.[15] This test obtains close to 90% sensitivity and specificity for maldigestion secondary to exocrine pancreatic insufficiency.[13] Patients are asked not to eat corn or fibre-rich products the day before the test, to have breakfast at least 2 hours before the test, not to smoke in the 6-8 hours before or during the test and not to do physical exercise. For the test, patients ingest two small pieces of toast and 20 g of butter with a substrate mixture of 250 mg of 13C mixed-triglyceride in powder form, 200 mL of water and 10 mg of metoclopramide. A baseline breath sample is taken at 20 minutes and thereafter every 30 minutes for 6 hours (12 measurements in total). Duodenal hydrolysis induced by pancreatic lipase causes the labelled metabolites to be absorbed and metabolised by the liver, and $13CO_2$ is expelled in the breath. Infrared spectrophotometry is used for the analysis and a mathematical programme calculates the percentage substrate recovered.

Alcohol Liver Disease

Chronic alcohol consumption is associated with varying degrees of liver disease, ranging from simple fatty liver (steatosis) to confirmed cirrhosis. Alcohol is metabolised in the liver via the cytosolic dehydrogenases, cytochrome P450 and peroxisomes.[16] Liver damage occurs as a result of alcohol oxidation in this organ and of an imbalance in the redox mechanisms, as well as a consequence of increased oxidative stress caused by the same oxidation process or due to an absence or deficiency of certain antioxidants. Although there is a close link between the amount and duration of alcohol intake and the occurrence of hepatic lesions, only around 30% to 40% of alcohol users have clinically significant liver damage.[17]

Pancreatic Insufficiency, Chronic Pancreatitis and Chronic Liver Disease: Coincidence or Shared Toxicity?

Few studies have analysed the prevalence of pancreatic insufficiency and chronic pancreatitis in patients with liver disease. Using the faecal elastase test, Aparisi *et al*.[18] calculated that 7% of patients with cirrhosis had pancreatic insufficiency, compared to 14.8% of asymptomatic alcoholic patients.

It has been estimated that fewer than 5% of alcohol-consuming patients develop chronic pancreatitis.[19-21] Previous studies have indicated cirrhosis to be present in between 5% and 30% of patients diagnosed with chronic pancreatitis.[22] Angelini *et al*.[11] found that 12.5% of patients with chronic alcoholic pancreatitis also had findings for liver cirrhosis, but did not associate histological findings for the liver (extent of fibrosis) with the severity of pancreatic insufficiency.

The Aparisi[18] study mentioned above, which used the faecal elastase test to diagnose exocrine pancreatic insufficiency and the indocyanine green clearance test to diagnose liver failure, pointed to an inverse relationship between hepatic and pancreatic function in patients with chronic alcoholic pancreatitis and cirrhosis. The authors, concluding that alcohol usually damages a single organ, found no association between insufficiencies in the two organs.

In the same vein, Hayakawa *et al*.[22] reported a negative correlation between liver and pancreatic function in alcohol consumers diagnosed with chronic liver disease. The same authors also observed increased pancreatic secretion in patients with alcoholic liver disease.

A number of studies have pointed to the existence of hypersecretory states for pancreatic juice — as measured by the secretin test — in patients with chronic alcoholic liver disease.[23, 24] This pancreatic juice contained less protein and calcium and so protected the pancreas from the formation of protein plugs and calcifications.[22, 25] Dreiling *et al*.[26] formulated the hypothesis regarding the hypersecretory pancreatic state in cases of alcoholic cirrhosis, mentioning the possibility that a hypersecretory state in alcohol users with liver disease may be due to reduced inactivation of secretin or an outcome of portal hypertension.[22, 23] The hypersecretory state has also been encountered in animal models; low protein levels were found in the pancreatic juice of rats that were administered high amounts of alcohol, a situation which reversed after the alcohol was withdrawn.[24] The same study found that chronic alcohol intake altered neurohormonal control of the pancreas, especially in central sites involving the extreme area and at the acinar cell level with large quantities of alcohol. Chronic alcohol intake in large amounts was associated with pancreatic protein hypersecretion mediated by central vago-vagal disinhibition pathways and also occurring at the acinar cell level. The suspension of alcohol intake partially reversed the neurohormonal dysregulation of the liver function. These data support a model of rats that are chronically administered high doses of alcohol and which have an enhanced susceptibility to hyperstimulation and hypersecretion, especially during the abstinence phase. Hyperstimulation combined with alcohol-induced lowering of the acute pancreatitis threshold may combine to trigger acute pancreatitis episodes in alcoholics and may eventually lead to chronic pancreatitis.[24]

Sakai *et al*.[27] who administered the cholecystokinin-pancreozymin test, concluded that the prevalence of pancreatic insufficiency was greater in patients with chronic liver disease of any etiology and that there were no differences between patients with and without cirrhosis.

The medical literature includes no studies based on using the mixed-triglyceride breath test to detect exocrine pancreatic insufficiency, and furthermore, includes few studies that distinguish between patients with and without cirrhosis.

Few studies have evaluated the existence of chronic pancreatitis and pancreatic insufficiency in a population with chronic liver damage due to alcohol intake.[12, 18] Our working group[28] determined the prevalence of exocrine pancreatic insufficiency and chronic pancreatitis in patients with chronic liver disease caused by alcohol, and assessed the factors possibly associated with their development. In this observational study, patients with alcoholic liver disease were compared with a group of subjects with chronic non-alcoholic liver disease. All patients were asked to perform the 13C mixed-triglyceride breath test. Patients who reported abdominal pain were evaluated for chronic pancreatitis by endoscopic ultrasonography in accordance with diagnostic criteria as defined by Wiersema[29] (four or more criteria determine a diagnosis of chronic pancreatitis). Indeterminate or suggestive cases of chronic pancreatitis were excluded. This study demonstrates a high prevalence of pancreatic insufficiency (55.2%) and chronic pancreatitis (44%) in subjects with chronic alcoholic liver disease. Pancreatic insufficiency appears to be more common in the early stages of liver disease, as demonstrated by findings of lower prevalence in patients with cirrhosis (46.2% vs. 70%, $p = 0.017$) and is inversely associated with liver failure (albumin, INR, prothrombin time and thrombocytopenia) and portal hypertension (ascites, splenomegaly and gastroesophageal varices) parameters. These findings have not previously been reported in studies that do indicate that alcohol usually only affects a single organ (either liver or pancreas).[18, 30] The fact that a pancreatic hypersecretion state has been described in patients with alcoholic liver disease[22-24, 26] may explain the finding that patients with cirrhosis have a lower prevalence of pancreatic insufficiency compared to those without cirrhosis. It is widely accepted that alcohol is a risk factor for chronic pancreatitis.[17] The strong correlation existing between chronic pancreatitis and abdominal pain would tend to lead to a suspicion of this disorder in patients with this symptom, so such patients should undergo endoscopic ultrasonography once other possible

causes of abdominal pain are ruled out. This study is the first that used the 13C mixed-triglyceride breath test as a diagnostic method for exocrine pancreatic insufficiency in alcoholic liver disease patients, unlike previous studies, which have analysed faecal elastase, directly obtained pancreatic juice and urinary n-benzoyl-tyrosyl-para-aminobenzoic acid.

By improving clinical, laboratory and nutritional parameters, pancreatic supplements may play an important role in the treatment of patients with pancreatic insufficiency. However, more studies are needed to assess the benefit of diagnosis and treatment of pancreatic insufficiency in this population.

In conclusion, patients with chronic alcoholic liver disease seem to have a higher prevalence of pancreatic insufficiency and chronic pancreatitis —most especially patients who have not yet developed cirrhosis with liver insufficiency or portal hypertension. In our study, liver function and portal hypertension parameters were inversely correlated with pancreatic insufficiency and chronic pancreatitis. Abdominal pain was frequently associated with an endoscopic ultrasonography finding of chronic pancreatitis and was present in patients with chronic non-cirrhotic liver disease. Patients without cirrhosis frequently had more episodes of acute pancreatitis. In our study, we found no association between smoking and chronic pancreatitis and so we did between diarrhoea and pancreatic insufficiency.

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Diffuse Liver Disease: The Role of Ultrasound, Elastography and Histology

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Introduction

Chronic viral and non-viral hepatopathies are frequent in daily clinical practice and the evaluation of patients with chronic diffuse liver diseases often represents a challenge. Usually we start with clinical assessment, followed by biological tests and ultrasound (US) examination and, classically, with liver biopsy (LB), for grading and staging the severity of liver disease.

The clinical evaluation is often irrelevant. The biological assessment by means of usual tests is also often irrelevant regarding the severity of the liver disease, but specific biological tests for the evaluation of activity or fibrosis, such as ActiTest-FibroTest or FibroMax, are useful.[1]

Ultrasound Evaluation of the Liver

Ultrasound evaluation of the liver can offer more information, for instance regarding the severity of steatosis or revealing signs of cirrhosis. But the question is: can ultrasound evaluation have a role for staging the liver disease? In a prospective study performed by D'Onofrio *et al*.[2] on 105 patients with chronic hepatitis, the results of US for the evaluation of hepatic fibrosis were compared to LB. The authors evaluated the following US parameters: liver margins, parenchymal echo-pattern, portal vein caliber and spleen diameter, and concluded that US diagnosis of at least severe fibrosis and cirrhosis in chronic liver disease is possible with 25% sensitivity, 100% specificity, 100% positive predictive value and 79% negative predictive value, with a total diagnostic accuracy of 80%. Thus, US evaluation is useful for the diagnosis of advanced liver disease, when the echo-pattern is modified, and the spleen size and portal vein caliber are increased. The same conclusion was reached by Zheng *et al*.,[3] who studied the value of US for the evaluation of liver fibrosis in comparison with histology in 225 patients with chronic viral hepatopathies. They found that the hepatic parenchyma echo-pattern, the liver surface and the thickness of the gallbladder wall are independent predictors of liver fibrosis. In this study, the diagnostic accuracy of US for compensated cirrhosis was 80.7%.

Liver Biopsy

Liver biopsy (LB) has a key role for the diagnosis of chronic diffuse hepatopathies.[4-7] According to Fontolliet,[4] LB has the following roles: to confirm the diagnosis of chronic hepatitis; to assess the necro-inflammatory activity (grading) and the severity of fibrosis (staging); to exclude another cause of hepatopathy or an associated disease and to certify the diagnosis of cirrhosis, when present.

Currently LB is considered to be the reference method for the evaluation of chronic liver diseases, however it is not a perfect method. There are some problems regarding the diagnosis of cirrhosis by LB[8] and regarding the differences in fibrosis severity, when twin LB are performed in both liver lobes.[9]

Another question is how representative for the whole liver is a needle biopsy? The size of the LB specimen varies between 1 and 4 cm in length and between 1.2 and 1.8 mm in diameter, representing approximately 1/50,000 of the total mass of the liver.[10] Its size, especially the number of portal tracts, is essential for a correct diagnosis. In a systematic review regarding the quality of LB specimens, including more than 8,700 patients, in more than half of cases the LB specimens had an average length and number of portal tracts well below the published minimum sample size requirements (only 42% of LB performed with a large 17-gauge needle contained 10 or more portal tracts).[11]

Last but not least, there are problems concerning the safety of LB. In a large multicentre retrospective study that included 98,445 LB, severe adverse events occurred in 3.1‰ of the cases and the mortality rate was 0.3‰.[12] In another large study the mortality rate due to fatal haemorrhage was 0.11%,[13] while in an older retrospective study on 68,276 LBs, death was infrequent (0.09‰).[14] LB complications are related to the technique, being more frequent when the blind technique is used: Younossi *et al*.[15] found a 4% complications' rate in "blind" biopsies vs. 2% in US-guided biopsies (the study also proving that US-guided LB is cost-effective). Considering the operator's experience, Gilmore *et al*.[16] showed that the complications' rate is much higher in inexperienced operators (less than 20 biopsies performed), as compared with skilled operators (more than 100 biopsies) (3.2% vs. 1.1%).

Considering all of the problems mentioned above, LB is not

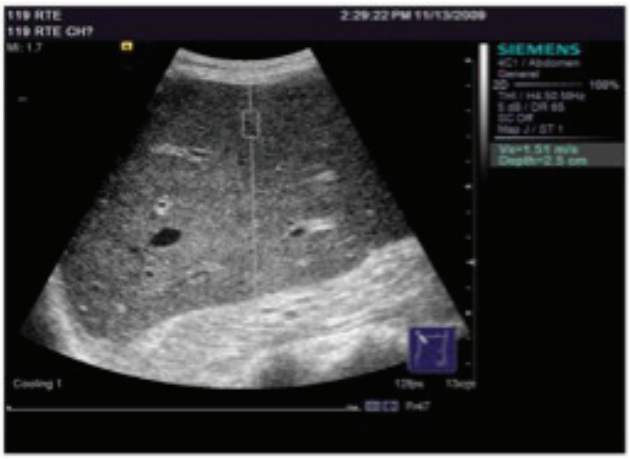

Figure 1. Ultrasound ARFI measurement in the liver acquired from the right intercostal space.

unanimously accepted by patients and physicians. In a French study, in which 1,177 general practitioners were interviewed, 59% of HCV patients refused the LB, an opinion shared by 22% of the physicians.[17] Thus, the non-invasive assessment of liver fibrosis by serologic and elastographic methods can be a solution in those patients.

Elastographic Methods

The elastographic methods based on ultrasound waves, and used for the evaluation of liver fibrosis, can be divided into:[18]

1. Shear waves Elastography
• Transient Elastography (TE) (FibroScan);
• "Point" Shear waves Elastography - Acoustic Radiation Force Impulse (ARFI) quantification (Siemens, Phillips);
• Real-Time Shear Waves Elastography (SWE) – (Supersonic Imaging, Aixplorer system).
2. Strain Elastography, or quasi-static elastography (Hitachi RT-E).

Shear Waves Elastography

Transient Elastography (FibroScan)

Transient Elastography (FibroScan) is a method already used for more than 10 years for liver fibrosis evaluation, initially for the evaluation of chronic hepatitis C. Further studies proved this method's value in other chronic hepatopathies, such as chronic hepatitis B, haemochromatosis, primary biliary cirrhosis, chronic co-infection with human immunodeficiency virus (HIV) and hepatitis C virus, or non-alcoholic steato-hepatitis (NASH).

The studies published until now showed that TE is not accurate enough to differentiate among contiguous stages of fibrosis (especially between F0-1 and F2), but is sensitive enough to differentiate between the absence and mild fibrosis from significant fibrosis and cirrhosis, essential for the decision regarding treatment.

Several meta-analyses assessed LS measurements by TE as a predictor of significant fibrosis (≥F2) in patients with chronic hepatopathies.[19-22] In the Friedrich-Rust meta-analysis,[19] the mean AUROC was 0.84, with a suggested optimal cut-off of 7.6 kPa for detecting significant fibrosis (F≥2) and AUROC 0.94, with an optimal cut-off of 13 kPa for predicting cirrhosis. In a more recent meta-analysis published by Tsochatzis[22] which included 40 studies, the summary sensitivity and specificity for predicting significant fibrosis were 0.79 and respectively 0.78. The mean optimal cut-off was 7.3±1.4 kPa (mean 7.2 kPa). For predicting liver cirrhosis, the summary sensitivity was 0.83 and the summary specificity was 0.89, and the mean optimal cut-off was 15±4.1 kPa (mean 14.5 kPa). In the same study an analysis regarding the etiology of liver disease was also performed.[22] Data regarding patients with chronic hepatitis C were extracted from 14 studies, and the summary sensitivity and specificity were 0.78 and 0.80 respectively for predicting significant fibrosis. Data regarding patients with chronic hepatitis B were extracted from 4 studies, and the summary sensitivity was 0.84 and the summary specificity was 0.78.

TE was also studied for predicting liver cirrhosis complications, especially portal hypertension. The AUROC's for predicting clinically significant portal hypertension were 0.945 -0.99, with cut-offs varying between 13.6 - 21 kPa.[23-25] Also, the correlation of TE measurements with HVPG measurements, was higher for patients with HVPG>12mmHg, than those with HVPG≤12mmHg.[26]

Acoustic Radiation Force Impulse (ARFI) Quantification Technique (Figure 1)

Similar with TE, ARFI was first used and validated in patients with chronic hepatitis C, and afterwards in others etiologies of chronic liver diseases. Published studies found LS cut-offs assessed by ARFI ranging from 1.21 to 1.34 m/s for predicting significant fibrosis (F≥2), with AUROC's ranging between 0.85-0.89,[27-30] while for predicting cirrhosis the ARFI cut-offs ranged between 1.8-2 m/s, with AUROC's between 0.89-0.93.[27-31]

In a retrospective international multicentre study comprising 181 patients with chronic hepatitis B and 91 with chronic hepatitis C, the correlation of LS as assessed by ARFI elastography with histological fibrosis was significantly better in patients with chronic hepatitis C, as compared with those with chronic hepatitis B: r=0.653, p<0.0001 vs. r=0.511, p<0.0001 (p=0.007).[32] The mean LS values corresponding to each stage of fibrosis were similar in patients with chronic hepatitis B and C.

In a recently published meta-analysis by Friedrich-Rust *et al*., which evaluated 8 studies including 518 patients with chronic hepatopathies, the AUROC of ARFI elastography for predicting significant fibrosis (F≥2) was 0.87, for predicting severe fibrosis (F≥3) it was 0.91 and for predicting cirrhosis it was 0.93.[33] When 312 patients with chronic hepatopathies were comparatively evaluated by means of ARFI and TE, the AUROCs for predicting

Figure 2. SWE measurement in the liver in a normal subject, acquired from the right intercostal space.

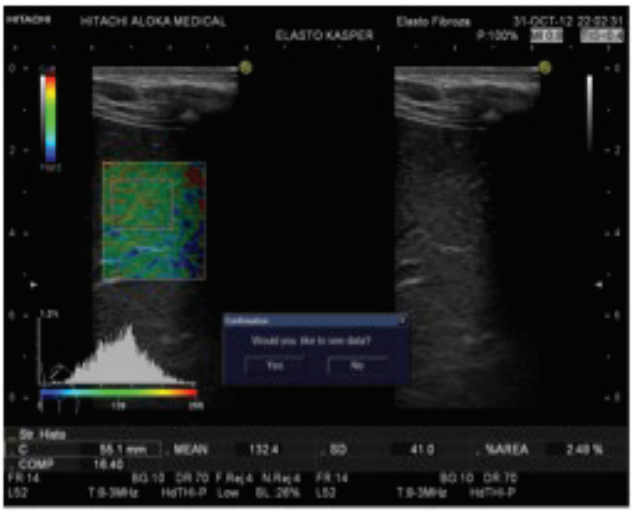

Figure 3. Histogram evaluation in RT-E.

significant fibrosis and cirrhosis were significantly higher for TE as compared with ARFI, while for predicting severe fibrosis they were similar.

ARFI elastography was also evaluated as a predictor for liver cirrhosis complications, especially for portal hypertension. In a small study including 48 patients (36 cirrhotic), Salzl *et al*. found a good correlation of LS assessed by ARFI with HVPG measurements (r=0.709), the AUROC for predicting clinically significant portal hypertension being 0.874.[34]

Real Time Shear Wave Elastography (SWE) - SuperSonic Imaging Technique

Similar with ARFI, SWE can be used in patients with ascites. Another advantage of this method is that the measurements' results are displayed both in colour code superimposed on a standard B mode US image, and as numeric values (expressed either in m/s or in kPa) (Figure 2).

The largest study assessing this system included 133 patients with chronic hepatitis C, who were evaluated by means of SWE, TE and, in a subgroup of patients, also by means of LB. The AUROCs for elasticity values assessed by SWE were: 0.948 for F≥2, 0.962 for F≥3 and 0.968 for F=4. In this study, the AUROCs for SWE were better than those for TE for F≥2, F≥3 and F4.[35]

Ferraioli *et al*. compared SWE with TE and LB. The cut-off value found for F≥2 was 7.4 kPa (AUROC=0.91), for F≥3 it was 8.7 kPa (AUROC=0.99) and for F=4 it was 9.2 kPa (AUROC=0.97). In cases in which SWE was compared to TE, the two methods showed similar diagnostic performance.[36]

Because only a few studies were published, more information is needed for the introduction of this method in clinical practice.

Strain Elastography - Real-Time Elastography (RT-E)

This is a colour coded elastographic method for stiffness evaluation, in which external compression is needed for tissue stimulation in order to obtain an elastogram (Figure 3).

Recent Japanese studies[37, 38] showed good results for the evaluation of liver fibrosis with this system. Yada *et al*. evaluated 245 patients with chronic hepatitis C and B in which liver biopsy (LB) was used as the gold standard.[37] Nine parameters from the histogram were used based on which Liver Fibrosis Index (LFI) was calculated. In this study, the AUROC of LFI was 0.800 to discriminate between F0-1 vs. F2-4 and 0.846 to discriminate between F0-3 vs. F4. In another study, Fujimoto K *et al*. compared LFI to LB in a cohort of 310 subjects. LFI highly correlated with fibrosis stage (r=0.68 with p<0.001) and the AUROC of LFI to discriminate between F0-1 vs. F2-4 was 0.82.[38]

Conclusion

In conclusion, elastographic methods, especially Transient Elastography, are increasingly used in daily practice for liver fibrosis assessment. In the near future, they will probably decrease the need for liver biopsy in patients with chronic liver diseases.

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The Impact of Capsule Endoscopy in Obscure Gastrointestinal Bleeding and its Value in Predicting Bleeding in the Long-term

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Introduction

Obscure gastrointestinal bleeding (OGIB) is defined as bleeding of unknown origin from the digestive tract that persists or recurs without an obvious etiology after a normal esophagogastroduodenoscopy and colonoscopy. Endoscopic examinations must be performed at least twice with ileum intubation in these patients.

OGIB has been divided into two categories: occult and overt, based on the absence or presence of bleeding. Overt OGIB is defined as visible GI bleeding (eg, melena or haematochezia) and can be categorised further as active (ie, evidence of ongoing bleeding) or inactive bleeding.[1] OGIB represent approximately 5% of all GI haemorrhages.[2,3] The source is localised in the small bowel in approximately 75% of these patients, but it may occur anywhere throughout the GI tract.[1]

There are many etiologies of OGIB. Angiectasias (Figure 1) of the small bowel are the most common reason in older patients.[4]

Non-steroidal anti-inflammatory drugs (NSAIDs) enteropathy and inflammatory bowel disease have been associated with erosions, ulcers, and strictures (Figure 2) of the small bowel and therefore are also causes of OGIB.[5,6] Most common causes of small bowel ulcers are NSAIDs and Crohn's disease (Figure 3).

In our unpublished data, between January 2005 and January 2012, CE (PillCam SB, Given Diagnostic Imaging System, Yoqneam, Israel) reports of 196 patients were retrospectively evaluated. Benign small bowel ulcer rate was 13.3% and etiology could not detected in 41% of these patients by surgical resection or biopsies by double balloon enteroscopy. During the mean 32.2±23 month follow-up period, no other reasons were detected and iron replacement was given. Since the treatment approach is unclear, idiopathic small bowel ulcers are still an important problem in clinical practice. The other causes of small bowel ulcers and OGIB are shown in Table 1 (Figure 4-5).

During the last decade, small bowel diseases were clearly defined by the development of new techniques. Indeed, capsule endoscopy (CE) became especially popular because it is a non-invasive imaging method.[7,8]

CE has a higher diagnostic yield than other diagnostic modalities and improves the diagnostic yield in patients with OGIB. Most investigators, therefore, agree that CE should be the first step of investigation for OGIB and it is accepted as the first-line technique in patients with OGIB in American Gastroenterological Association (AGA) guideline (Figure 6).[9]

The diagnostic yield of CE in OGIB is extremely variable in different studies.[10-14] Subgroup analysis in these studies show that the diagnostic yield is much higher in overt bleeding group (92%) than in the occult bleeding group (44.2%). Furthermore, it has been reported that significant small-bowel pathology may be missed during CE examinations, but can be subsequently diagnosed using alternative diagnostic tools including double-balloon enteroscopy (DBE). Especially, large submucosal lesions (such as GIST) can be missed by CE.[15,16] There are many factors that influence the diagnostic accuracy in CE examination from small bowel cleaning to operator experience and patients' characteristics. Current data suggest that timing of the procedure is the main important factor. International consensus on capsule endoscopy (ICCC) meeting recommended that CE should be performed in 2 weeks after bleeding starts.[17]

Besides all of these findings, CE can change the management of patients and can affect the clinical outcome positively. There are some reports about CE's effect on clinical outcome in recent years. Pennazio *et al.*[10]

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reported that sensitivity, specificity, positive and negative predictive values of CE were 88.9%, 95%, 97%, and 82.6%, respectively in OGIB patients. In this study, the highest yield of CE was obtained in active bleeding patients (92.3% vs 44.2%). On the other hand, lowest yield of CE was observed in previous overt bleeding patients (12.9%). Therefore, CE should be performed as soon as possible after active bleeding in OGIB patients.

Alberts *et al*.[18] evaluated CE findings of 247 patients in a multicentre study. They found that CE findings changed the clinical management of 66% of patients. Similarly, another recent study reported that definitive treatment was changed in 70% of the patients positively diagnosed by CE.[19] On the other hand, according to a study by Rastogi *et al*., positive clinical outcome was observed in only 16% of patients.[20] In a large meta-analysis including 227 studies with 22.840 procedures (66% for OGIB), diagnostic yield of CE was found to be 61%.[21] All of these findings showed that clinical management is easy and fast with CE in OGIB patients. However, selection of patients is very important. In our routine clinical practice, rate of double balloon enteroscopy need is 7.1% after CE.

CE is also useful for the long-term outcome of OGIB. Several studies evaluated the clinical implications of negative CE results over the long-term. However, there are contradictory findings regarding the

Figure 1. Vascular ectasia in OGIB patient in an old male.

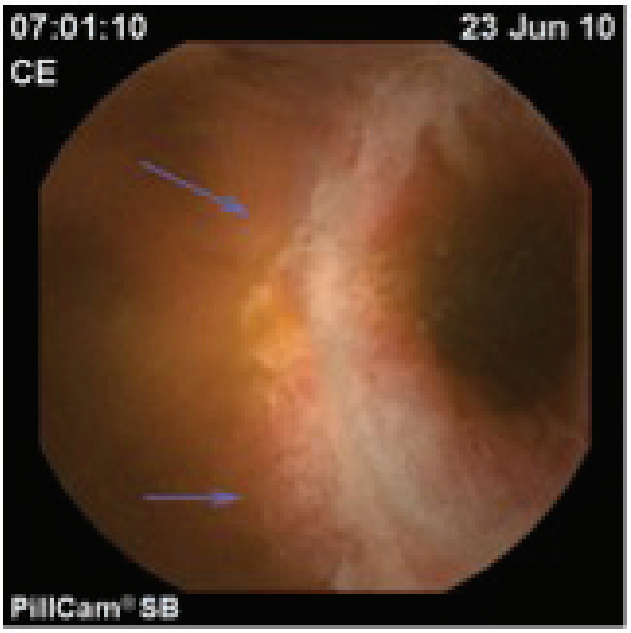

Figure 2. Non-specific diaphragm like ulcer in the absence of NSAIDs in a young female (confirmed by surgical specimen).

Figure 3. Crohn's disease patient presented with OGIB with unsuccessful ileum intubation in a young male (confirmed by biopsies taken by double balloon enteroscopy).

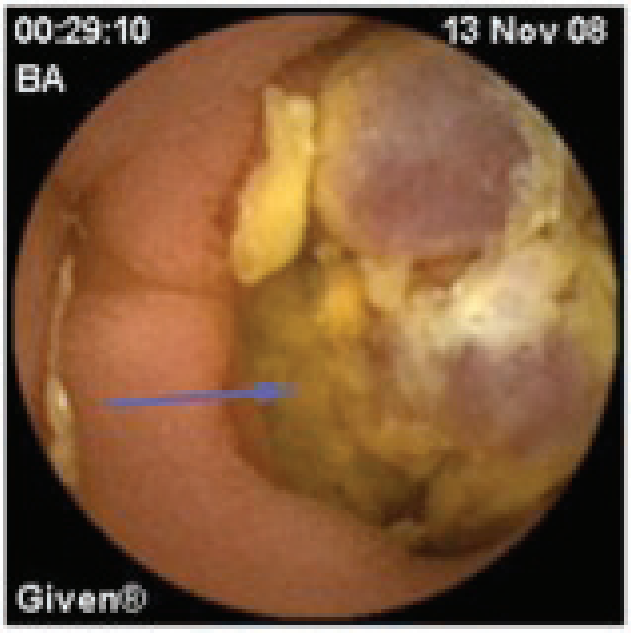

Figure 4. Malign melanoma in a young female (confirmed by surgical specimen).

Figure 5. Neuroendocrine tumour mimicking gastrointestinal stromal tumour with the presence of central ulcer in a young female (confirmed by surgical specimen).

long-term outcome in patients with OGIB and prediction of re-bleeding after negative CE.[22-24]

Lai *et al*.[22] followed 49 patients for a median of 19 months (12-31 months). 63.3% of these patients were capsule positive (possible bleeding lesions were detected) and 36.7% were capsule negative. Re-bleeding rate was 32.7% (n: 16) in the first year. They showed that patients with OGIB and negative CE had a very low re-bleeding rate. Delvaux *et al*.[25] reported CE results of 44 patients in the 12-month follow-up period. CE positive predictive value was 94.4%, and the negative predictive value was 100% in patients with normal CE findings. Fujimori *et al*.[26] determined that the possibility of re-bleeding was 5% in patients with positive CE results. Arakawa *et al*.[27] study showed that none of the cases of normal CE suffered re-bleeding. Iwamato *et al*.[28] reported that re-bleeding rate was significantly higher in overt OGIB patients (26.1%) than the others (4%) in CE negative 78 OGIB patients during the 6-month follow-up period.

All of these studies evaluated the impact of CE in the short-term of follow-up. In our study group, 141 OGIB patients' CE reports were evaluated and 90% of the cases demonstrated positive lesions. In the long-term follow-up period [median follow-up period was 36 months (6-82 months)] only one CE negative patient re-bled. The sensitivity and specificity of CE in predicting re-bleeding are 100% and 93%, respectively.[29] In addition, most of the studies comprise of small numbers of patients and have short-term follow-up.

In many studies, the main predictive factor for re-bleeding is the presence of comorbidities, especially as portal hypertension, renal failure, and ischemic heart disease. Small intestine vascular lesions were observed to have a high probability of re-bleeding compared

Ulcers	Peptic (ectopic gastric mucosa, ZES) Crohn's Disease Ulcerous jejunoileitis in celiac disease Drugs (NSAIDs, potasium, thiazides, gold, cocaine, etc) Gastroesophageal Reflux Disease Infectious Disease (CMV, Mycobacterium, Campylobacter, Shigella, Fungus) Cryptogenic Multifocal Ulcerous Stenosing Enteritis Collagen Diseases (Behçet's disease, vasculitis, otoimmune enteropathy) Amilodiosis
Vascular	Angiodysplasia Dieulafoy lesion Varices Lymphangiomas
Tumours	Polyps Carcinoid Lymphoma Gastrointestinal stromal tumour Carcinoma
Other	Diverticulosis Meckel's diverticulum Hemobilia Hemosuccus pancreaticus Aortoenteric fistula

Table 1. Causes of OGIB. ZES = Zollinger Ellison; NSAIDs = Nonsteroid anti-inflammatory Drugs; CMV = Cytomegalovirus.

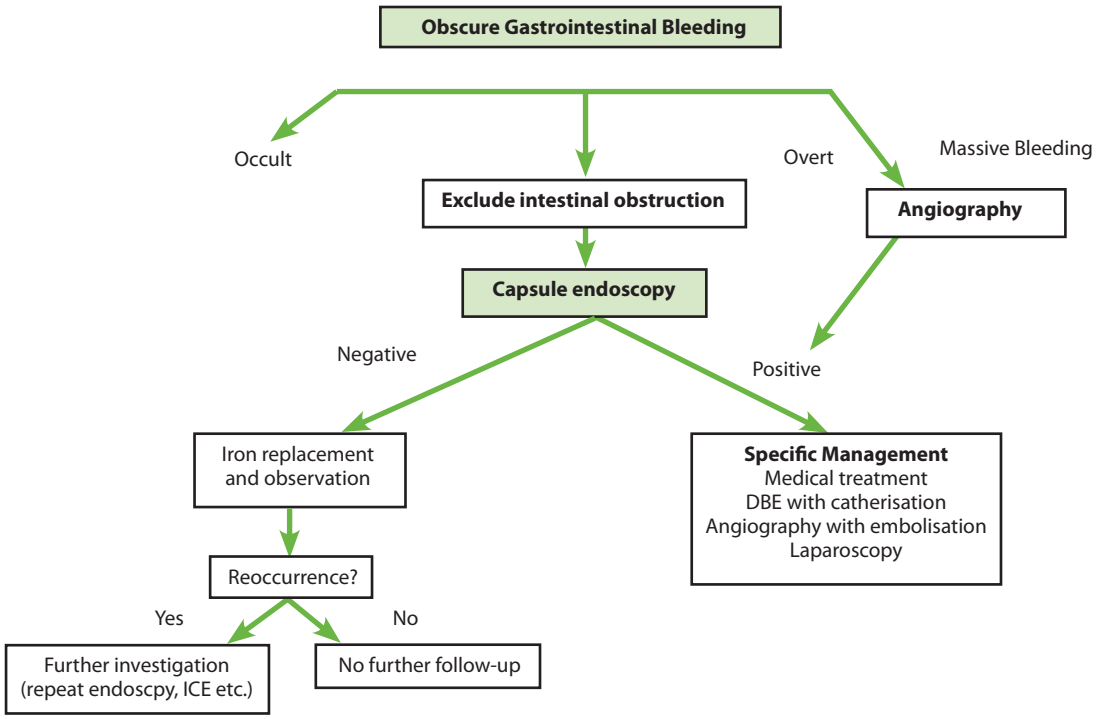

Figure 6. Algorithm for the diagnosis and management of obscure GI bleeding (modified by AGA guideline). IOE: intraoperative enteroscopy; DBE: double balloon enteroscopy.

to the non-vascular small intestine diseases.[27]

A recent study showed that second look CE may be useful after initial negative CE in the overt re-bleeding patients.[30] However, cost effectivity is not acceptable for these patients and double balloon enteroscopy should be performed by oral plus anal route in the second look. However, some studies with limited number of patients showed that diagnostic capability of second CE (35-75%) can be acceptable and some benefits can be obtained in OGIB patients who had negative initial C.[30-33] Obscure occult bleeding patients with normal CE should be managed conservatively without further investigations according to International consensus on capsule endoscopy (ICCC) guidelines.[31] Conservative management means a wait and see policy. Meanwhile, iron supplements can be given and if necessary blood transfusions may be used for symptomatic treatment. If the patient has overt bleeding or a need for transfusion, further investigation is required. Double-balloon enteroscopy should be used as mentioned above.

Some studies showed that re-bleeding rate was low during the first year[21, 24] and that it increased in the long-term.[34] In the Park *et al.*'s study, re-bleeding rate was reported as 35.7% at the end of median follow-up period, which was 31.7 months (12-58 months). They concluded that these patients should be closely observed.[24]

In the Koh *et al.*'s study, re-bleeding was observed after one year in half of the patients.[34] Therefore, the diagnostic yield of CE should be evaluated in the long-term of period. The summary of re-bleeding rates and follow-up periods from different studies in the literature are shown in Table 2.

If the patient selection is right for the initial CE as our study group, the diagnostic capability of CE is very high and can predict re-bleeding with high-sensitivity and specificity even in the long-term follow-up.

Study	Cases (n)	Follow up duration (months); median/mean (range)	Re-bleeding (%)
Lai *et al.*[22]	49	19 (12-31)	6
Park *et al.*[24]	51	32 (12-58)	36
Delvaux *et al.*[25]	44	12 (10-29)	0
Loranceau Savale *et al.*[35]	35	15 (11-26)	0
Joon Koh *et al.*[34]	51	23 (6-89)	23
Iwamato *et al.*[28]	78	20 (6-37)	4
Akyuz *et al.*[29]	141	36 (6-82)	8
MacDonald *et al.*[23]	49	17±6 (12-NA)	11

Table 2. Re-bleeding rates after negative CE and follow-up periods from literature.

In conclusion; the possibility of visualisation of the small bowel has improved with CE. Re-bleeding rate is low in long-term period in the CE negative OGIB patients. However, on the basis of these studies close follow-up for at least 2 years is needed in patients with OGIB even in the presence of negative CE findings. Meanwhile, negative CE is a good predictor for re-bleeding in the long-term follow-up period.

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Pancreatic Cancer – A Stem Cell Disorder?

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Introduction

Pancreatic cancer is one of the deadliest malignancies, accounting for over 220,000 deaths per year worldwide, and the incidence in developed countries is increasing at an alarming rate. Despite progress in imaging techniques, surgery, and chemotherapy for pancreatic cancer, only 5% of the patients survive beyond 5 years after diagnosis. Over the last 3 decades, several risk factors for pancreatic cancer have been identified, including male sex, old age, smoking, obesity, chronic pancreatitis, and a family history. Several candidate genes are related to pancreatic cancer, including BRCA2, PALB2, CDKN2A, STK11, and PRSS1, and germ-line mutations are associated with a substantially increased risk in humans.[1-8] Nevertheless, the exact pathomechanisms underlying the malignancy are not fully understood. Therefore, it seems reasonable to state that despite intensive scientific and clinical efforts, pancreatic cancer remains a very mystifying disease that presents a great challenge from both a scientific and clinical standpoint.

Wojciech Błogowski graduated from the Faculty of Medicine at the Pomeranian Medical University in Szczecin, Poland. He has attained the degree of habilitated doctor in the field of medicine. His research interests are transplantation and regenerative medicine as well as obesity. Dr. Błogowski's achievements have earned him numerous international awards and honours, including the "National Scholar Award" from the United European Gastroenterology Federation and a "Top 10 Abstract Award" from the American Society of Transplant Surgeons.

Mariusz Z. Ratajczak is the Henry and Stella Hoenig Endowed Chair in Cancer Biology, Director of the Developmental Biology Research Program at the University of Louisville's James Graham Brown Cancer Center and the Head of the Department of Physiology at Pomeranian Medical University in Poland. Professor Ratajczak is an internationally known investigator in the field of adult stem cell biology. He is a member of Polish Academy of Art and Science, has published over 400 peer-reviewed papers and is a recipient of several prestigious national and international awards. He is a section editor in *Leukemia* and editorial member of several journals including *Stem Cells* and *Journal of Clinical Investigation*.

Teresa Starzyńska received her medical degree *summa cum laude* from the Pomeranian Medical University of Szczecin, Poland. She is a Professor of Medicine and the Chairperson of the Department of Gastroenterology. She has worked as a Research Fellow at the German Cancer Research Center in Heidelberg and the Paterson Institute for Cancer Research in Manchester. She has published more than 100 original papers. Prof. Starzyńska's research has earned her awards from national and international scientific committees. Currently, her team is working on an EU grant on stem cells. She is also involved in studies on endoscopic submucosal dissection as a treatment for gastrointestinal malignancies.

The Concept of "Pancreatic Cancer Stem Cells" and its Significance

The clonal evolution model is the traditionally accepted model to explain cancer development and growth. According to this model, cancer cells develop over time from cells with multiple mutations, resulting in a population of "immortal cells." However, recent research suggests that malignancies such as pancreatic cancer may be a stem cell disorder.[9-12] It has been shown that tumours are composed of heterogenic cells, not all of which are capable of inducing tumour growth or promoting metastasis. In fact, only a very small percentage of pancreatic adenocarcinoma cancer cells can give rise to tumours, promote their systemic spread in immunodeficient animals, are capable of self-renewal, and differentiate into all other cancer cell types. In the literature, the cells that initiate pancreatic cancer are termed pancreatic cancer stem cells (PCSCs) and are believed to be at the top of the hierarchy of all cancer-forming cells.[13-16] Unfortunately, very little is known about the molecular characteristics of PCSCs, and only a few features of PCSCs have been proposed. It is generally believed that the strongest candidates for PCSCs are cancer/stem cells that express the following:

1. Surface markers such as CD24, CD44, CD133, ESA, and PANC-1, and the chemokine receptors CXCR4 (the receptor for chemoattractant stromal-derived factor-1 [SDF-1]) and/or c-Met (the tyrosine kinase receptor for hepatocyte growth factor [HGF]).
2. Some intracellular functional markers such as aldehyde dehydrogenase 1 (ALDH1), which interact at different molecular levels (epigenetic, translational, and/or transcriptional) in PCSCs, and they may make PCSCs more resistant to chemotherapy and enhance their proliferative potential.[13, 14, 17-20]

Experimental observations show that PCSCs constitute less than 1% of all cancer cells in the pancreatic environment.[13] In addition to the challenge of fully defining the exact molecular repertoire of PCSCs,

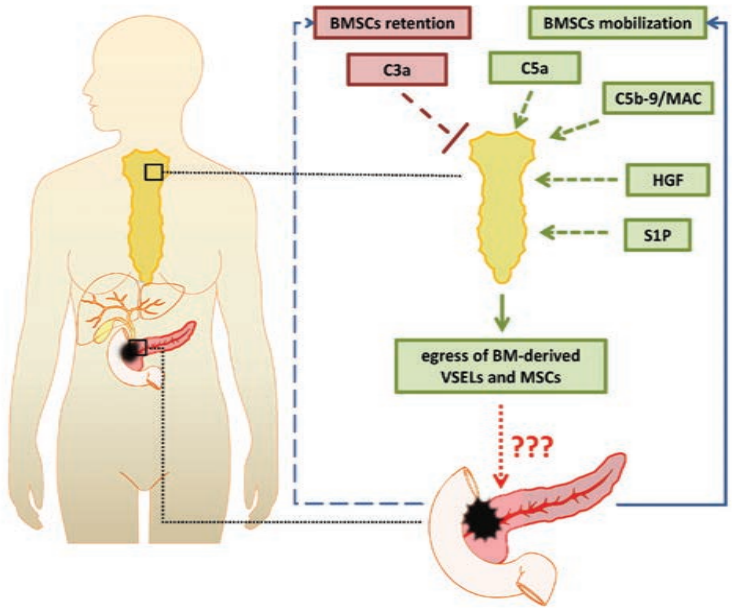

Figure 1. Simplified illustration of the mechanisms underlying the mobilisation of bone marrow-derived stem cells into the peripheral blood of patients with pancreatic cancer. BMSCs – bone marrow-derived stem cells; HGF – hepatocyte growth factor; MAC – membrane attack complex; MSCs – mesenchymal stem cells; S1P – sphingosine-1-phosphate; VSELs – very small embryonic/epiblast-like stem cells.

In patients with pancreatic cancer, there seems to be a "pancreatic-bone marrow" axis. In the course of the development of pancreatic adenocarcinoma, multiple changes occur in the systemic levels of factors promoting bone marrow-derived stem cell (BMSC) egress. Patients with pancreatic cancer have higher plasma levels of C5a and C5b-9/membrane attack complex (MAC) than healthy individuals. These molecules seem to promote the egress of BM-derived cells via stimulation of granulocytes within the BM, which secrete proteases and disrupt pro-homing signaling mediated by stromal-derived factor-1 and CXCR4. In addition, C5b-9/MAC interacts with various cells (e.g., erythrocytes and platelets) and leads to the release of sphingosine-1-phosphate, which also seems to promote the egress of BMSCs. Among the various growth factors, hepatocyte growth factor is significantly elevated in the peripheral blood of patients with pancreatic cancer and it is correlated with the absolute numbers of circulating BM-derived very small embryonic/epiblast-like stem cells and mesenchymal stem cells. The question remains whether the BMSCs released from the BM migrate to pancreatic tissue in patients with pancreatic cancer.

there is another very intriguing scientific question – where exactly do these cells originate?

Bone Marrow-derived Stem Cells: Occasional Bystanders or Drivers of Pancreatic Cancer Development?

It is hypothesised that PCSCs may not only originate from the pancreas, but may also be recruited from the bone marrow (BM).[21] Several types of stem/progenitor cells showing diver properties have been identified in human BM. The bone marrow-derived stem cell (BMSC) population most commonly used in medicine are cells enriched for CD34+CD45+ haematopoietic stem/progenitor cells (HSPCs), which are blood-forming cells that are transplanted to treat congenital blood forming disorders and haematological malignancies.[22] However, from an oncological point of view, the most interesting BMSC populations are those that may contribute to the development and progression of solid organ malignancies, for example, CD45-CD90+CD105+ mesenchymal stem cells (MSCs) or CD45-CD34+KDR+ endothelial progenitor cells (EPCs).[23, 24]

For the last few years, our team has concentrated on analysing the systemic changes in the circulation of various BMSC populations in patients with pancreatic cancer, with a particular interest in the recently discovered novel population of Lin-CD45-CD133+CXCR4+ very small embryonic/epiblast-like stem cells (VSELs). These VSELs are a small population of pluripotent stem cells that express embryonic transcription factors characteristic for pluripotent stem cells such as Oct-4 and Nanog, and that express certain genes 100-times higher than for example HSPCs, enabling them to trans-differentiate into almost any organ or tissue derived from all 3 germ layers.[25-29] Our research showed that in patients with pancreatic adenocarcinoma, circulation of BM-derived MSCs and VSELs is high. In contrast, other populations of BMSCs such as HSCs or EPCs do not seem to be mobilised into the peripheral blood in the course of pancreatic malignancy.[30] This phenomenon of increased circulation of BMSCs in patients seems to be associated with systemic activation of one of the most primitive immune response mechanisms (complement cascade), sphingosine-1-phosphate and hepatocyte growth factor/c-met axis signaling (depicted and described in detail in Figure 1).[31-37] In humans, the terminal portion of the complement cascade anaphylatoxins/molecules (C5a and C5b-9/membrane attack complex [MAC]) strongly correlates with the absolute numbers of mobilised VSELs and MSCs.[30] This is in agreement with previous studies in which the (cancer) cells seem to migrate toward increased levels of C5a and Cb5-9 that are present in areas of neoplastic effusions.[38] Interestingly, the systemic mobilisation of BMSCs in patients with pancreatic cancer seems to be an early phenomenon in the course of pancreatic adenocarcinoma development, as the absolute numbers of circulating BMSCs are similarly elevated in patients with both early diagnosed and advanced disease.[30]

Unfortunately, thus far no one has been able to fully demonstrate the migration of circulating BMSCs to pancreatic tissue in patients with pancreatic cancer in a clinical setting. However, some recent data provide evidence supporting our observations that BM-derived VSELs and MSCs may contribute to the development and progression of human pancreatic adenocarcinoma. Several studies have provided strong evidence that BMSCs may contribute to the development of various malignancies, including those located in the gastrointestinal tract.[39-44] In several animal studies, it has been shown that various BMSCs may migrate into pancreatic tissue, become incorporated into pancreatic structures, and trans-differentiate into pancreatic exocrine structures.[41-44] This phenomenon has been observed in both physiological pancreatic regeneration/development and pathologic situations such as chronic

pancreatitis and pancreatic cancer. During the development of malignancy, BMSC mobilisation also seems to be critical for the induction and maintenance of systemic "immunosuppression" towards the developing tumour, and multiple structural changes within the microenvironment that are crucial for evasion of the immune system (reviewed in detail in reference 42). Pathological analysis of human pancreatic specimens derived from patients with pancreatic adenocarcinoma showed significantly higher infiltration of CD133+ cells with high nuclear expression of Oct-4 protein in malignant pancreatic tissues.[45] Interestingly, such cells appear to be quite similar to our population of BM-derived VSELs. Experimental studies have shown that the murine pancreas, similar to other organs (not constituting the gastrointestinal tract, such as the heart, kidney, and brain), harbours a population of Lin-Oct-4+Sox-1+ VSELs.[46] Moreover, MSCs and VSELs are involved in the creation of tumour stroma and vessels, as well as in the systemic metastatic propagation of prostate tumours in animals.[47] Although these results have not been confirmed in pancreatic adenocarcinoma to date, it seems likely that they may also apply to pancreatic cancer development in humans, and VSELs may be an overlooked link in carcinogenesis.[48-50]

The Clinical Significance of PCSCs and the Novel Practical Approaches Derived from PCSC Research

These recent results have led to significant progress in the development of potential novel diagnostic and therapeutic options, which are currently being validated in preclinical studies and are soon expected to enter clinical trials. The initial characterisation of PCSCs enabled scientists to concentrate on a very specific population of cells and carefully examine them at a molecular level, which has helped in identifying additional targets that will be assessed using newly developed systemic drugs directed towards PCSCs. The use of isolated PCSCs could also be used in the clinical setting for diagnostic and prognostic purposes. For example, isolated PCSCs could be used *ex vivo* to predict a patient's response, or to detect resistance to chemotherapeutic drugs. Such an approach would enable physicians to personalise therapy for each patient without exposing the patient to the potential side effects of systemic chemotherapeutic treatment. While thus far no reagents directed towards PCSCs have been tested in humans, some inhibitors of signaling pathways and molecules expressed on PCSCs have showed some effectiveness when combined with gemcitabine in preclinical studies (Quercetin, DDL4 blocking antibodies, or γ-secretase inhibitors).[51-53] Promising candidates for such drugs are inhibitors of the HGF/c-met axis (drug XL184), which considerably reduce the tumour burden in mice.[18] Since growing tumour may also chemoattract circulating stem cells that may provide stroma and vessels it would be important to inhibit the incorporation of such cells into expanding tumour tissues.[47] Moreover, our observations from clinical studies indicate the complement cascade, specifically C5a and C5b-9/MAC, together with sphingosine-1-phosphate signaling as factors that may mobilise into peripheral blood several types of stem cells potentially involved in vascularisation and stromalisation of pancreatic adenocarcinoma.[30] Clinical application of drugs interfering with these pathways seems to be a possibility, as various complement inhibitors have already been developed and introduced into the clinical repertoire, e.g., eculizumab in a haematological and transplantation setting.[54-57] In addition, a synthetic analogue that interferes with sphingosine-1-phosphate signaling (fingolimod/FTY720) showed some promise in experimental studies on pancreatic cancer cells,[58, 59] and has been approved for treating systemic sclerosis.[60] Importantly, these compounds seem to be relatively well-tolerated by patients, and present limited toxicity.[61]

Although therapeutic and diagnostic applications are underway, new scientific challenges seem to be arising, and several concerns will need to be addressed. First, researchers will undoubtedly need to concentrate on a full molecular characterisation of the exact population of PCSCs in humans, and to check whether the cells are indeed BM- or pancreas-derived VSELs. Second, it would be of great interest to define the exact role and significance of the egress of BMSCs from the BM in patients with pancreatic cancer. Are these cells our enemies or, paradoxically, allies in the fight against cancer? To answer such questions, multiple genetic studies of VSELs and MSCs will need to be performed, including analyses of their epigenetic status. Finally, clinically applicable methods for BMSC and PCSC visualisation *in vivo* will need to be developed. Once these issues are addressed, we can be sure that these exciting challenges will drive the research forward over the next years and may offer novel therapeutic options for the patients.

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Esophageal Stenting in Closure of Benign Leaks, Perforations and Fistulas

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Perforation of the esophagus is a challenging and life-threatening complication associated with significant morbidity and mortality rates. Its three main causes are: anastomotic leakage, spontaneous during vomiting (Boerhaave syndrome) and endoscopy-related perforation.[1]

The mortality rate of esophageal perforation is high, ranging from 10% to 30% in most studies, and is higher in intrathoracic perforations than in cervical perforations.[2-5]

The management of a patient with an upper gastrointestinal leak is complex and often involves treatment of sepsis, organ failure and nutritional deficits, in addition to treating the underlying leak.

Successful management depends on an early diagnosis and prompt treatment. However, after surgery, a diagnosis of leak is often difficult to establish and, in other cases, diagnosis depends on physician's alertness.[6]

The classic treatment options include surgical repair, esophagectomy, or cervical exclusion. When it is possible, primary surgical closure and mediastinal drainage within 24 hours of the injury have shown to improve survival rates.[7, 8] However, if the diagnosis is not early enough, surgery carries high morbidity and mortality, particularly in patients with mediastinal and pleural contamination. These patients may be preferably treated conservatively because mortality from a surgical intervention equals that of a conservative approach.[9] It is accepted that patients with limited contamination, without manifestations of evolving sepsis and organ failure, can be safely treated with nil by mouth, intravenous fluids, simple drainage and antibiotics.[10] In a 10-year retrospective study by Hasan *et al*., conservative management of esophageal perforation had a survival rate of 84.6%. However, in this study mortality rate was 15%, with chest infections as the most common complication in 46% of cases.[11]

The management of larger defects, especially when associated with significant contamination, tissue loss, and systemic sepsis is more difficult. In the setting of large anastomotic leaks, or in overt sepsis requiring drainage, surgical treatment is indicated because conservative treatment is mostly unsuccessful.[12-14] In spite of current advances, mortality from clinically apparent thoracic leakage remains high with these traditional management options, commonly approaching 50%.[15-22]

Self-expanding metal stents (SEMS) are indicated to palliate symptoms associated with malignant esophageal obstruction.[23, 24] SEMS are usually covered by silicone, and various types have been developed. These covered SEMS are currently used in the treatment of malignant esophageal fistulas with excellent results and good short-term quality of life. This treatment is considered the standard approach to malignant perforation and fistulas.[18, 25-28]

There are two kinds of covered SEMS: fully covered (FC-SEMS) which are fully covered by a sillicon cover, and partially covered SEMS (PC-SEMS) where the silicon covers only the central part of the stent.

The use of these SEMS is a theoretically attractive approach to benign esophageal perforations, but prior reports about SEMS placed for benign esophageal diseases speculate on the possibility that the risk of complications and potential lack of removability could be high.[20, 29]

Endoscopic therapy of esophageal perforations aims to restore continuity of the esophagus for early feeding, prevent contamination of the mediastinum, and facilitate re-epithelialisation of the esophageal wall defect. However, it is important to emphasise that even if stenting is able to effectively seal esophageal leaks or ruptures and allows healing of the esophageal wall, when there are fluid collections in the mediastinum or pleural cavity concurrent adequate drainage is mandatory. The key to a successful outcome is prompt recognition of leak with rapid esophageal stenting immediately after the perforation. This should be combined with adequate debridement and drainage of pleural and mediastinal fluid collections. Broad-spectrum antibiotics should also be given in those patients with pleura-mediastinal collections.[30, 31]

The main drawbacks of stent placement are stent migration and tissue

in/overgrowth, both of which require repeated interventions.

The first clinical case of a benign perforation due to a Boerhaave syndrome treated by a covered SEMS (Wallstent PC-SEMS) was described by Adam *et al*. in 1995.[32] The patient presented an esophageal perforation that was diagnosed 3 weeks after the onset of the symptoms. A surgery had failed in solving the perforation and the clinical status of the patient had deteriorated due to sepsis, which meant that he was not suitable for surgery and so they decided to stent this patient. The patient initially presented a good evolution, sealing the leak and solving the sepsis. However, 8 weeks after the procedure, the patient died because of a massive haematemesis due to an extensive esophageal necrosis.

Later, in 1996 Dumonceau *et al*.[33] reported recurrent stricture owing to the development of tissue ingrowth throughout the uncovered portion of the stent. In these initial cases they hadn't removed the prosthesis after the perforation solved. This is why these authors recommended early stent removal in order to minimise the occurrence of stricture.

The first clinical case of benign perforation due to a Boerhaave syndrome successfully treated by a PC-SEMS that could later be removed was described by Davies *et al*. in 1999. However, this stent was a PC-SEMS, which was not designed to be removed and which they had to remove it in a piecemeal fashion with a rigid esophagoscope.[34]

These difficulties in removing PC-SEMS usually happen because hyperplasia tissue in/overgrowth on the uncovered parts at both ends can make those PC-SEMS difficult to remove.[5-38]

Since then, many clinical cases and series have been published, where authors have used different stent designs and materials in order to make stent removal easier.

To assess these problems, three different strategies have been published:

1. The use of plastic expandable stents (SEPS): SEPS are self-expanding plastic stents made of a polyester net embedded in silicone. They have some theoretical advantages over SEMS because it is supposed that these SEPS have the ability to be extracted without damaging the esophagus, presenting fewer tissue reactions. However, SEPS have some disadvantages, in that they are more cumbersome to use because they need manual assembly prior to use i.e. before using this stent, it is necessary to load it in the insertion device.

Another disadvantage of these stents is that they need a wider insertion device than SEMS and this requires more frequent dilation before delivering these plastic stents. This delivery system is also less flexible than the one of SEMS. On the other hand, there is a significanly higher migration rate and probably a lower success rate with SEPS.[38-45]

2. The use of FC-SEMS could also solve the problem. It has been published that these stents are easily removable even after 6 weeks of treatment.[46] On the other hand, and because hyperplastic tissue is not usually present in FC-SEMS, they could theoretically present a higher migration rate.[39, 47, 48] These excesively high migration rates occurred mostly in the initial studies published with FC-SEMS, where FC-SEMS without flared flanges were used (i.e. Alimaxx-ES).[48, 49] Some recently developed stents or FC-SEMS (Hanarostent, Walflex, Evolution, Bonastent, Niti-S) are designed with flared flanges (i.e. "dog-bone" shaped flares) to prevent such migration.[50] Moreover, some of these recently developed FC-SEMS are designed with proximal (or proximal and distal) sutures, thus providing a means to reposition or remove the stent (i.e. Hanarostent, Wallflex, Evolution, Niti-S, Bonastent).

3. Some authors like Swinnen *et al*.[39] prefer the use of PC-SEMS to close perforations. When the fistula has been closed it is quite usual to have problems to remove these stents because a severe hyperplastic tissue ingrowth may occur in the non-covered parts of the stent. This situation occurs especially after more than 6 weeks of treatment.[39] To address this problem, they recommend inserting a plastic stent (SEPS) inside the PC-SEMS for ten days, in order to induce a pressure necrosis of the hyperplastic tissue which could facilitate the removal of the PC-SEMS. However, this approach usually requires several extra endoscopic procedures to remove stents.

Various commercially available PC-SEMS, FC-SEMS and SEPS have been used for stenting in esophageal perforations (Table 1).

This way, initial case series with SEPS, FC-SEMS and PC-SEMS with limited number of patients showed successful resolution of benign stenosis and fistulas with few adverse effects and few cases of tissue in/overgrowth.[39-42, 46, 50-56]

Reactive non-malignant tissue in/overgrowth causes a problem mainly when stents are inserted for a longer period (more than 6-8 weeks) and has been reported to occur more commonly with PC-SEMS than with FC-SEMS or SEPS.[40, 48, 57]
Also, there have been some experiences in benign esophageal fistulas and stenoses treated with polydioxanone biodegradable stents.[58] However, these experiences are few, mostly in stenoses, and there are still some concerns about their safety.[59] This is why we think that they should only be used if other alternatives fail.

A recent systematic review by van Boeckel *et al*., evaluated various stents (FC-SEMS, PC-SEMS and SEPS) in the largest pooled analysis of all available studies evaluating the use of SEMS and SEPS in esophageal perforations or anastomotic leaks (it includes 267 patients and 25 studies).[60] The overall clinical success rate in healing the perforations after stent removal was of 85 without any difference between the three stent designs. This efficacy rate is higher than the

Name	Manufacturer	Material / covering	Diameter (mm)	Length (mm)	Delivery system size (mm)	Special features
Polyflex	Boston Scientific, USA	Polyester silicone covered (SEPS)	16-21	90-150	12-14	Needs manual assembly prior to stent placement
Ultraflex		Nitinol (PC- SEMS)	18	100-150	6	Available in proximal release.
Wallflex		Nitinol (PC & FC -SEMS)	18-23	103-155	6.17	
Wallstent		Stainless steel	20	100-150	6	
Niti S	TaeWoong Medica, Korea	Nitinol (FC-SEMS)	16-20	60-150	5.8-6.5	Proximal/distal release available. Proximal lasso.
Z-stent	Wilson-cook Medical USA	Stainless steel (PC-SEMS)	18	60-150	10	
Evolution		Nitinol (PC & FC -SEMS)	18-20	80-120	8	
Bonastent	Standard Sci-Tech, Korea	Nitinol FC-SEMS	18	60-150	5	Proximal and distal lasso.
Choostent / Hanarostent	M.I. Tech, Korea	Nitinol FC-SEMS	18-22	60-170	6	Proximal and distal lasso.
Alimaxx-ES	Alveolus, USA.	Nitinol FC-SEMS	22	70-120	7.4	Antimigration struts.
SX ELLA Stent Danis	ELLA-CS, Czech Republic	Nitinol FC-SEMS	20-25	85-150	8.9	Proximal lasso. Antimigration ring

Table 1. Commercially available esophageal stents used in esophageal perforations.

one described in the surgical series.[8] Stent-related complications were high (34%) and were caused by migration and tissue in/overgrowth. Overall mortality rate was 13%, which is lower than that reported due to surgical intervention.[61]

They conclude that stent placement for a period of 6-8 weeks is safe and effective for benign esophageal ruptures. Thus, these authors said that stenting should be considered as first treatment option in esophageal perforations and leaks because of its high clinical efficacy and minimally invasive nature. They did not find differences between the various stent types, so they think that stent choice should depend on expected risk of stent migration (SEPS and FC-SEMS) and, to a minor extent, on expected risk of tissue in/overgrowth (PC-SEMS).[60]

There are neither randomised comparative studies between FC-SEMS, SEPS and PC-SEMS to evaluate which stent is the best in terms of efficacy and lack of complications, nor comparative studies designed to know which one presents less difficulties to be removed. Van Halsema *et al*.[62] studied the safety of endoscopic removal of self-expandable stents after treatment of benign esophageal diseases. They performed 329 stent extractions in 214 patients. These patients suffered from different benign pathologies, presenting only 164 benign fistulas, leaks or perforations.

In this series, they used 58 SEPS and 236 SEMS (165 FC-SEMS and 71 PC-SEMS). Similar to other series, removal of PC-SEMS was associated with significantly more adverse events (24.5%) than FC-SEMS (3.5%; p=0.00) or SEPS (9.5%; p=0.08). The major conclusion of this study is that FC-SEMS should be preferred to SEPS and PC-SEMS in this setting.

There are no well-designed studies comparing surgical treatment and stenting to evaluate which is the best treatment. However, Biancari *et al*.[8] recently performed a big pooled revision analysis including 75 studies with 2,971 patients undergoing any treatment for esophageal perforation. They wanted to evaluate the efficacy of current treatments (surgery, conservative and endoscopic treatment), and identify variables associated with mortality following esophageal perforation. Pooled immediate mortality after primary repair was 9.5% (95% CI 7.1-12.1: 41 studies with 575 patients), after esophagectomy 13.8% (95% CI 9.2-19.2: 30 studies with 246 patients), after T-tube or any other tube repair 20% (95% CI 11.4-30.4: 11 studies with 118 patients), and after stent grafting 7.3% (95% CI 3.7-12: 18 studies with 262 patients). These results show that stent grafting may achieve slightly lower mortality rates. However, available studies may be biased by patient selection and limited experience of the surgeon. Further studies with more detailed data are necessary to identify risk factors associated with poor outcome and to better evaluate the efficacy of current treatment modalities.

Conclusions

Esophageal perforation is a life-threatening condition that must be recognised and addressed aggressively. The treatment of esophageal perforation is dependent on various clinical factors, technology, and the level of expertise available. Conservative management is possible for small and contained fistulas and in the event of aggravating underlying co-morbid illnesses, as long as there is no sepsis involved. Minimally invasive treatment or endotherapy is a viable option for most esophageal perforations. Endoluminal stenting is a minimally invasive therapy in case of anastomotic complication which is safe and effective. It results in rapid leak occlusion and avoids morbidity of reoperative repair. Surgical treatment is indicated for larger defects and in overt sepsis requiring drainage and in perforations involving diseased esophagus. The different treatment modalities of esophageal perforation are not exclusive of each other, but may be combined in the management of the condition. Further studies and technology may aim to improve the currently available endoscopic treatment modalities, and to develop novel techniques in the treatment of esophageal perforation.[61]

The role of endoluminal stenting in Peri-operative setting could be considered in situations such as:

1. Those patients with an anastomotic leak that are diagnosed late in the course and in whom operative closure is not feasible.
2. Those patients with an anastomotic leak with medical condition who are too precarious for surgical intervention.
3. Those patients with chronic fistula due to anastomotic failure.

In our practice,[46] we found that the fully covered retrievable stent with a diameter up to 22-25mm wide, should be used for effective sealing of the defect. There is a problem of peri-stent leak, especially from the jejunal limb in some cases. However, it is usually a contained leak which can be minimised by nasogastric tube with aspiration within the stent. It is very important to drain all the collections percutaneously or surgically. The major complaint about these stents is their high migration rate, but this is often a minor problem that can almost always be solved endoscopically.[46]

Sometimes, another stent has to be inserted across the previous stent for effective sealing. The inserted stent should be removed within 6-8 weeks.

However, it is necessary to perform further comparative prospective studies comparing surgical and endoscopic approaches to better evaluate which is the best option in those patients.

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Upcoming Congresses and Meetings

12th International Congress on Obesity (ICO)

17 – 20 March 2014

Kuala Lumpur, Malaysia

The 12th International Congress on obesity will present a programme which encompasses each of the main areas of obesity research and practise. The 8 main tracks will be From cells to systems, From genes and environment to pathophysiology, From healthy weight to weight-related pathologies, From nutrition, exercise, and psychology to lifestyle, From lifestyle intervention to drugs and surgery, From home environment to society: causes and consequences, From individual choice to population prevention: solutions and interventions and From evidence to policy. In addition to Plenary and the IASO Award Lectures, a series of symposia will be featured, focusing upon cutting-edge areas in obesity. These will include key topics such as adipose tissue fibrosis, the gut microbiome, epigenetics, bariatric surgery, obesity in children, lifestyle changing and maintaining, and how to get policy changed. Poster sessions will continue to be a key component of the congress, and the final Plenary Lecture immediately before the Closing Ceremony will be on a major breaking development in obesity research to ensure that the Congress is as up-to-the minute as possible.

SAGES 2014 Annual Meeting – Putting the Patient First

02 – 05 April 2014

Salt Lake City, USA

Society of American Gastrointestinal and Endoscopic Surgeons was founded in 1981 to foster, promote, support and encourage academic, clinical and research achievement in gastrointestinal endoscopic surgery. SAGES currently has more than 6,000 general surgeon members from countries around the world. The SAGES annual meeting is oriented toward minimally invasive surgery and, in 2013, had an impressive attendance of 2,400 surgeons. In 2014, the meeting continues a long-standing tradition of strong didactic sessions by experts, combined with exploration of innovative technology in the fields of general, upper GI, colorectal, endoscopic, robotic, and minimally invasive surgery. The programme will also highlight improved patient care with our first full-day course on enhanced recovery protocols, an interactive symposium on the ethics of innovation, and a return to common surgical procedures including bile duct exploration and ventral hernia repair. The programme will focus on relevant clinical problems that busy surgeons encounter every day in their respective practices including management of complications, approaches for reoperative surgical cases, and laparoscopy in the acute care setting, with all of the information gained from the meeting being easily adopted into daily clinical practise. In addition to a programme brimming with symposia and plenary sessions, the exhibition hall will showcase the latest equipment and instruments. This year, the hall will feature a new 'Spotlight on Hernia' area, which will incorporate a learning centre station, posters and industry products used to treat hernia repairs.

International Liver Congress™ 2014

09 – 13 April 2014

London, UK

The 49th annual meeting of the European Association for the Study of the Liver will offer an outstanding and attractive programme to enhance the scientific and educational contents for an ever growing number of international delegates. Last year's meeting attracted a record number of 9,612 participants, and the 49th Annual Meeting looks set to be even bigger. Highlights will include a clinical state-of-the-art lecture on Hormones and Obesity, 14 Joint workshops eminent Scientific organizations in the field of Liver Disease, 3 basic, 1 translational, and 8 clinical symposia including topics like "Diagnosis & assessment of Liver Cancer", "HIV and the Liver", "Controversies in Liver Transplantation", and "Prevention and control of Viral Hepatitis" and late-breaking abstracts. The Meeting will also feature the popular Abdominal Sonography Course.

Digestive Week 2014

03 – 06 May 2014

Chicago, USA

World Digestive Week is the world's largest gathering of physicians and researchers in the fields of gastroenterology, hepatology, endoscopy and gastrointestinal surgery. The meeting will provide attendees with top-quality educational sessions, abundant networking opportunities and the very latest research. World renowned doctors within the field will explore a variety of issues within these areas in satellite symposia and plenary sessions, and the meeting will also place a great emphasis on poster and oral presentations.

47th Annual Meeting of the European Society of Paediatric Gastroenterology, Heptology and Nutrition (ESPGHAN)

09 - 12 June 2014

Jerusalem, Israel

The 47th Annual Meeting of ESPGHAN is being jointly held by ESPGHAN and the Israeli Society for Paediatric Gastroenterology, Hepatology and Nutrition, and will include recent advances and

state of the art lectures covering genetic, immunological, microbioogical and clinical developments in the field of gastrointestinal disorders, liver diseases and nutritian. The meeting is a fantastic place to network with colleagues and discuss and share clinical and research interests with others.

14th World Congress of Endoscopic Surgery

25 – 28 June 2014

Paris, France

The 14th World Congress of Endoscopic Surgery will be held in Paris under the auspices of the European Association for Endoscopic Surgery (EAES), the International Federation of Societies of Endoscopic Surgeons (IFSES) and in conjonction with several other societies, including the SFCE (Société Française de Chirurgie Endoscopique, SAGES (Society of American Gastrointestinal and Endoscopic Surgeons), the Endoscopic and Laparoscopic Surgeons of Asia (ELSA), Asia Pacific hernia society, International Society for Laparoscopic ColoRectal Surgery (ISLCRS), Federación Latino Americana de Cirugia (FELAC), and Asociacion Latinoamericano de Cirugia Endoscopica (ALACE). This year, the theme of the congress is "Let the light shine", highlighting the wish that minimal access surgery not only encompasses endoscopic vision and techniques, but also represents the hopes and wishes of our patients to enjoy the benefits of minimally aggressive surgery with optimal outcomes. The congress will feature a variety of sessions, including 3D video sessions, face-to-face sessions, which will cover occlusion and colon cancer and incisional hemias amongst other topics, a wealth of lectures and consensus conferences. This looks set to be one of the most exciting congresses on endoscopic surgery for 2014.

ESMO 16th World Congress on Gastrointestinal Cancer

25 – 28 June 2014

Barcelona, Spain

The ESMO 16th World Congress on Gastrointestinal Cancer will provide important clinical updates, new findings, new techniques and updates on the latest research within the field of gastrointestinal cancer. The congress will feature a number of different sessions on topics such as gastric cancer, rare tumours, multimodality therapy and imaging. Highlights will include meet the expert sessions, satelight symposia and discussion sessions. The congress will also have a focus upon young medical oncologists, and will feature a range of sessions which will identify their interests and clinical needs.

22nd Annual Meeting of The Society for the Study of Ingestive Behavior (SSIB)

29 July – 02 August 2014

Seattle, USA

The Society for the Study of Ingestive Behavior (SSIB) is non-profit organisation which is committed to advancing scientific research on food and fluid intake and its associated biological, psychological and social processes. The Society provides a multidisciplinary environment for the free exchange of ideas and information, and serves as a resource for scientific expertise and education on topics related to the study of ingestive behaviour. The 22nd Annual Meeting will be an important congress that will cover a wide range of issues within this area of gastric medicine. Keynote speakers will include Barbara Cannon from The Wenner-Gren Institute, Stockholm, Micheal Schwartz from the University of Washington, Julie Mennella from the Monell Chemical Senses Center and Antonio Rangel from the California Institute of Technology and the programme will include plenary lectures, symposia, workshops and networking opportunities.

9th Scientific & Annual Meeting of European Society of Coloproctology

24 – 26 September 2014

Barcelona, Spain

Attendees of the 9th ESCP Scientific and Annual Meeting will be greeted with a newly enhanced educational programme which will be tailored towards both trainees and specialists in addition to the well-established scientific programme. The meeting will feature pre-congress workshops, industry workshops, symposia, keynote lectures, poster and oral presentations and clinical trails updates amongst others. Symposia topics will include intestinal polposis and non-IBD colitis, while exciting keynote lecture topics will include rectal prolapse and the role of microRNA in onset and progression of colorectal cancer. This looks set to be an exciting and thought-provoking event.

ESMO 2014 Congress

26 – 30 September 2014

Madrid, Spain

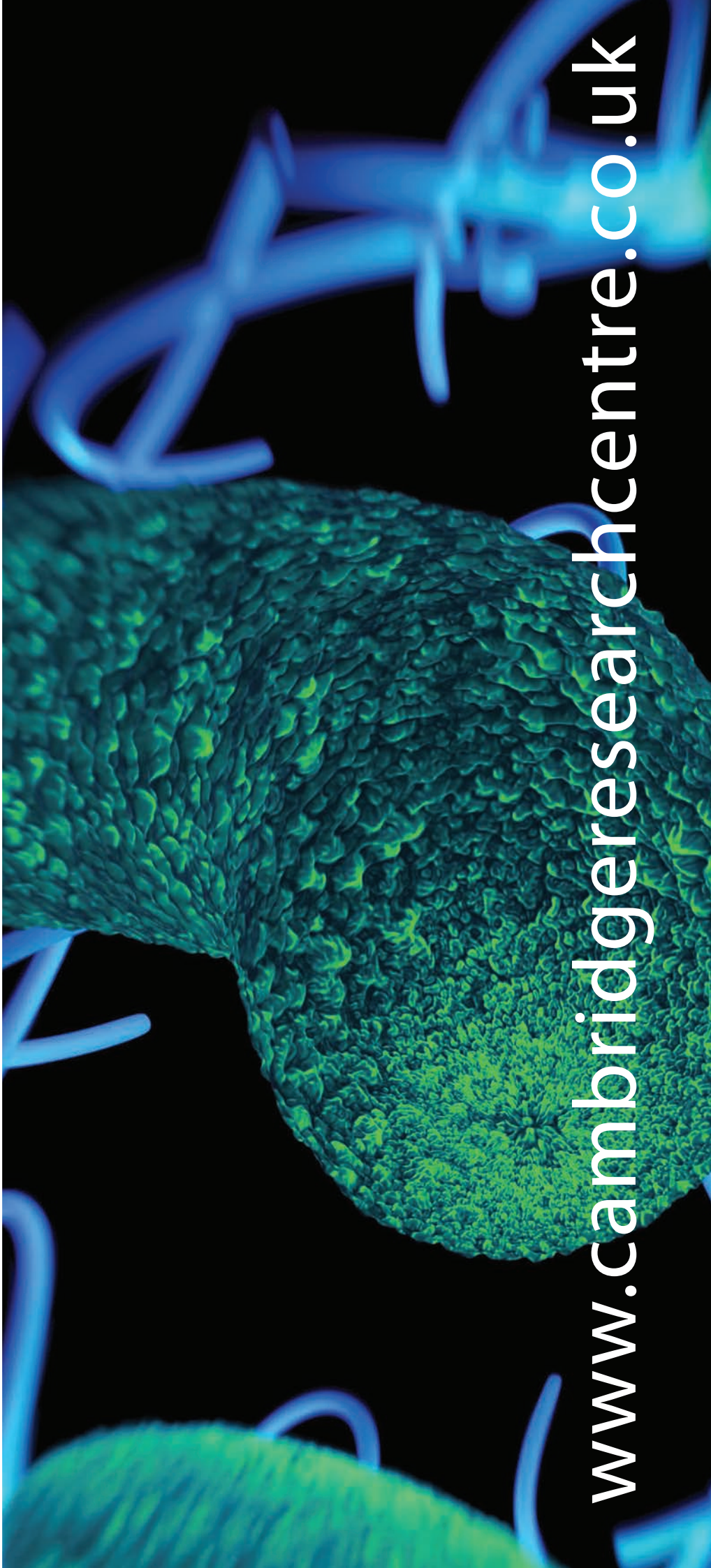
The theme for ESMO 2014 is 'Precision Medicine in Cancer Care' and, whether you are a medical or surgical oncologist, radiotherapist, immunologist or pathologist, the congress will offer you the tools to improve patient outcomes. This is the ultimate goal of ESMO 2014. Delegates will experience a detailed exploration of the practical, political and financial issues that stand between the ideals and reality of implementing optimal care for every patient suffering with cancer.

22nd United European Gastroenterology (UEG) Week 2014

18 - 22 October 2014

Vienna, Austria

Taking place for the 22nd time, UEG Week is the largest and most prestigious gastrointestinal meeting in Europe and is now a global congress. UEG Week attracts around 14,000 participants each year from around the world. The exciting experience for delegates will now be further enhanced by by an expanded and refined programme pathways, interactive clinical case symposia and a cutting-edge "Today's science; tomorrow's medicine". The packed programme will feature video case sessions and round table discussions, symposia, poster sessions and, as with the 2013 meeting, will also feature live endoscopy sessions. Networking is very much encouraged and UEG Week also offers the possibility to host side meeting to encourage this exchange of ideas.



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