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GASTROENTEROLOGY

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INSIDE

Review of

UEG Week 2013

Berlin, Germany

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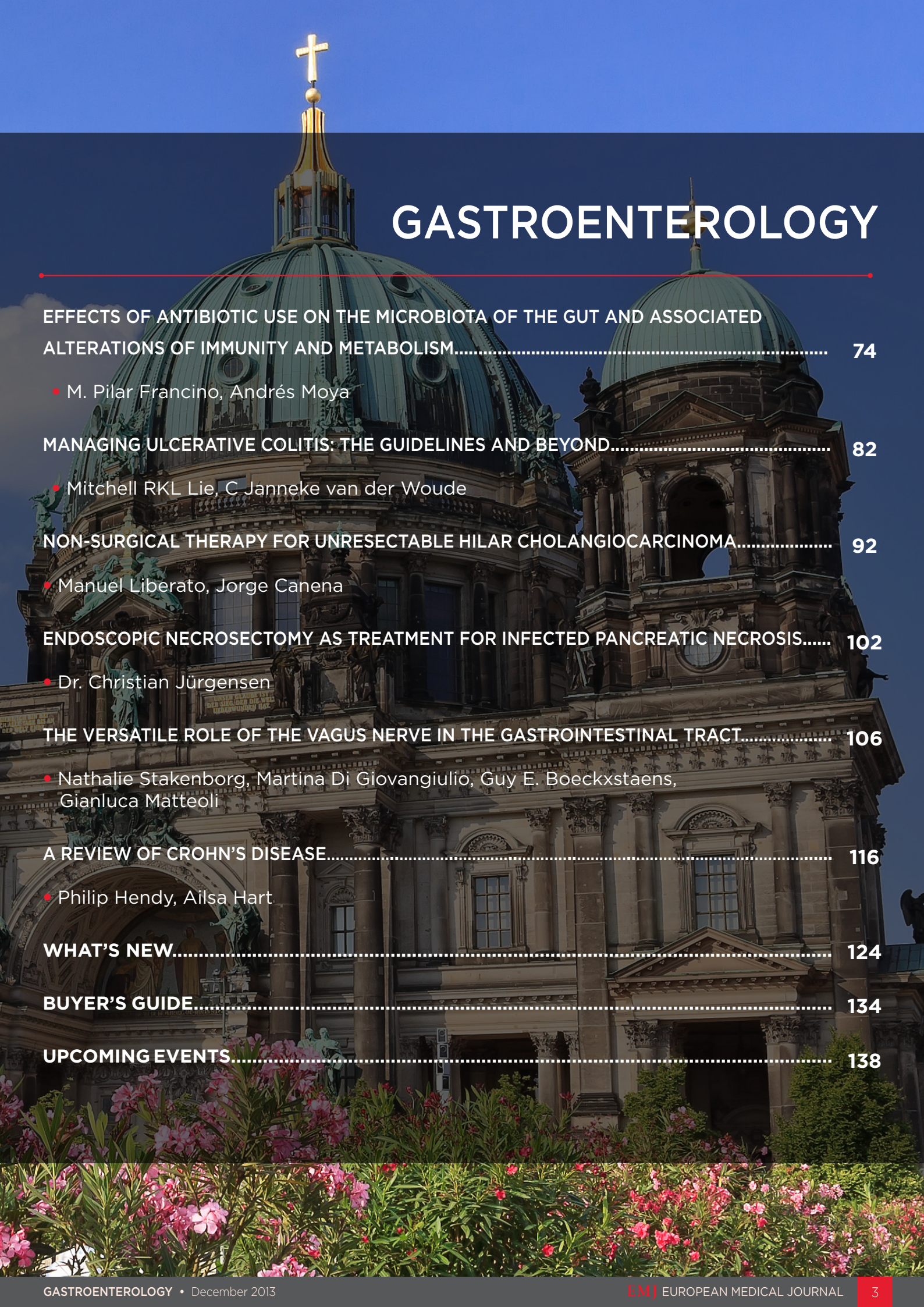

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EMJ GORELY NEW MEDIA

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Editor
Kelly-Ann Lazarus

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Medical Writing Assistance Provided By:
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GASTROENTEROLOGY

Robust protection against recurrent episodes of hepatic encephalopathy[1]

Daily treatment with XIFAXAN® 550* b.d. plus lactulose significantly reduces episodes† and hospitalisations‡ compared with placebo plus lactulose[1], and improves quality of life[2] as well as provides a cost-effective treatment option,[3] in patients with hepatic encephalopathy.

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References: 1. Bass, N.M., *et al.* N Engl J Med, 2010; 362(12): 1071-81. 2. Sanyal, A., *et al.* Aliment Pharmacol Ther, 2011; 34(8): 853-61. 3. Norgine data on file. 4. XIFAXAN® 550 Summary of Product Characteristics, 2012.

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NORGINE

Welcome

Kelly-Ann Lazarus

Editor, European Medical Journal

Welcome to the second edition of *European Medical Journal – Gastroenterology* which features a new and improved design and even more high-quality content. Alongside a continued stream of informative articles and news updates of the year in gastroenterology, our exclusive Congress Review section focuses on this year's UEG Week 2013, held in Berlin, Germany.

This year's meeting of gastroenterology specialists was particularly exciting in its programme, with a huge range of activities from seminars, post-graduate teaching programmes, and plenary sessions, to an exhibition hall buzzing with a host of exhibitors and poster presentations. John Atherton, the Chair of this year's UEG Scientific Committee explained: "We are continuing our efforts to make the meeting even more lively and interactive with voting sessions, clinical cases, debates and tandem talks, and this year are introducing more innovations including panel discussions and 'Chat with the Speakers' sessions." This interaction extended to live endoscopy sessions, which had been requested in feedback given by delegates in attendance to UEG Week 2012, and an Ultrasound Learning Centre, which provided individual, hands-on practice for both beginners and advanced users of the essential tool.

The meeting highlighted that causes of the diseases we aim to treat and cure remain unknown, and health-related quality of life of patients is in real need of improvement. The President of UEG, Colm O'Morain, commented that: "Addressing these issues makes the week a meeting of global consequence," highlighting the importance of UEG Week and the widespread effect it can have within the research for treatment of common diseases.

Awards, scholarships and prizes were awarded throughout the meeting in celebration and reward of the year's successes, and the most important new research findings were presented, ensuring a continued cycle of research, improvement, and success for the future.

Alongside our exclusive, in-depth review of UEG Week 2013, this journal features enlightened discussions on therapeutic targets and endoscopic enhancement technologies for the treatment of irritable bowel syndrome, surgical and non-surgical methods for specific conditions such as infected necrosis and unresectable hilar cholangiocarcinoma, and effects of antiobiotics on the microbiota of the gut, immunity and metabolism.

All in all, this edition of *EMJ – Gastroenterology* aims to provide readers with a range of subjects of interesting and insightful updates to keep them abreast of the year's advances in the gastroenterology field.

Kelly-Ann Lazarus

Editor, European Medical Journal

European Medical Journal - Gastroenterology is published annually.
For subscription details please visit www.emjreviews.com

UEG CONGRESS 2013

THE INTERNATIONALES CONGRESS CENTRUM BERLIN (ICC BERLIN), GERMANY

12TH-16TH OCTOBER 2013

Welcome to the *European Medical Journal* review of the 21st United European Gastroenterology Congress 2013

EMJ EUROPEAN MEDICAL JOURNAL

UEG CONGRESS 2013

THE INTERNATIONALES CONGRESS CENTRUM BERLIN (ICC BERLIN), GERMANY

12TH-16TH OCTOBER 2013

Welcome to the *European Medical Journal* review of the United European Gastroenterology Congress 2013

The 21st United European Gastroenterology (UEG) Week was the climactic event of 2013 in the field of gastroenterology. It attracted over 12,000 participants, 2,000 exhibitors, and over 3,500 abstracts were submitted from over 125 countries. The event took place from 12th-16th October 2013 in the Internationales Congress Centrum Berlin (ICC Berlin), which is considered to be one of the best and biggest congress venues ever built. The ICC Berlin is an artistically stunning building perfectly nestled in the capital city of Germany; a city which provided a perfect backdrop for the Congress by virtue of its combination of historical and contemporary allure.

UEG Week featured the most recent information regarding clinical issues and research pertaining to gastrointestinal and liver diseases. The themes of this year's congress included 'translating science into clinical practice' and 'GI and liver patient care: pathways, standards, guidelines'. There was a wide range of educational formats to excite both the most experienced gastroenterologists and those just entering into this wonderful field. Throughout the Congress there were live endoscopy demonstrations, video case sessions, and clinical case sessions, where the interaction of the audience formed the basis of opinion on issues from clinical images regarding the diagnostic approach.

John Atherton, Chairman, UEG Scientific Committee, highlighted in his welcome statement: "We are continuing our efforts to make the meeting even more lively and interactive with voting sessions, clinical cases, debates, and tandem talks and this year are introducing more innovations including

"There are many unmet needs in gastroenterology. The causes of many of the diseases we treat remain unknown and the quality of life of our patients leaves much to be desired. Addressing these issues make the week a meeting of global consequence."

Prof Colm O'Morain, UEG President

panel discussions and 'Chat with the Speakers' sessions."

Highlights also included the presentation of the UEG Research Prize which was awarded to Prof Ian Tomlinson, Wellcome Trust Centre for Human Genetics, Oxford, UK. The focus of his investigation was mainly on cancer predisposition. The turning point of his career was the identification of 20 genes which increase the likelihood of colorectal cancer. The UEG Lifetime Achievement Award was bestowed upon Prof Giovanni Gasbarrini, University of Bologna, School of Medicine, Italy, for his revolutionary work on *Helicobacter pylori* and other digestive diseases. Awards were presented in various categories to recognise the efforts of those that continue to contribute to the alleviation of gastroenterology-related diseases.

Some of the key topics discussed were issues relating to inflammatory bowel disease (IBD), Germany's Colorectal Cancer screening programme, interferon-free therapy to fight the hepatitis C virus, prevalence of chronic pancreatitis, gluten sensitivity, and pancreaticoduodenectomy.

Prof Colm O'Morain, UEG President, mentioned in his pre-congress statement: "At this meeting positive health will be emphasised and abstracts presenting the cutting edge of research and innovation will be presented. There are many unmet needs in gastroenterology. The causes of many of the diseases we treat remain unknown and the quality of life of our patients leaves much to be desired. Addressing these issues make the week a meeting of global consequence."

Colorectal cancer screening programme saves thousands of lives

NATIONWIDE success regarding the colorectal cancer (CRC) screening programme with colonoscopy, which took place in Germany, found high rates of cancer detection and low rates of complications. Overall, this analysis was deemed a success as thousands of individuals were potentially saved.

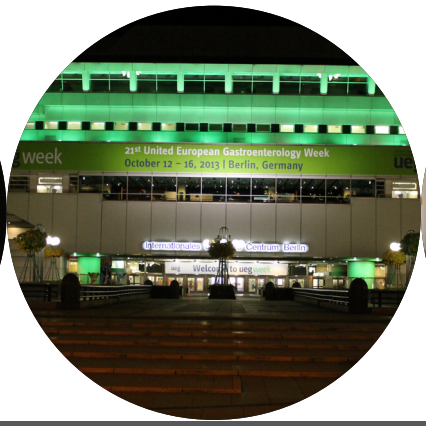
Demographically, CRC is considered the second most common cause of cancer-related deaths in Germany; each year, approximately 70,000 new cases of CRC are diagnosed. It is also considered to have one of the highest incidence rates in Europe. CRC screening throughout Europe is mainly detected through faecal occult blood testing, with Germany being the first country to introduce a nationwide colonoscopy screening programme.

Patient participation was free for anyone with health insurance, and coverage extended to 90% of the population. Also, individuals who are 55 years or older are entitled to screening and if the result is negative, it is repeated every 10 years.

According to Dr Christian Pox, Medical University Clinic, Bochum, Germany, speaking at UEG Week 2013, the successful key factor was the skill level of participating endoscopists and analysis of the results. He said: "Any endoscopist wanting to take part in the screening programme in Germany must fulfil very strict requirements."

The screening programme involved the analysis of 2.8 million colonoscopies between January 2003 and December 2008. Although participation rates were somewhat low, the detection rates were exceptional. Statistically, 1 in 100 people had early-stage asymptomatic cancer and 1 in 5 had adenomas which are CRC precursors. It was also found that men were more likely to have adenomas and less likely to undergo screening than women.

To improve participation rates, the first nationwide advertising campaign was launched by the Felix Burda Foundation which aimed to remove the taboo surrounding the screening programme and emphasised the benefits of colonoscopy screening. Currently, 6 million people have participated, which has led to the overall success of the programme and the decrease in mortality rates in Germany.

Critical analysis in the diagnosis of alcoholic liver disease

ASSESSMENT and follow-up of alcoholic liver disease (ALD) are current topics of debate, with arguments raging as to whether histology-based or non-invasive methods are preferable. Prof Karoline Lackner, University of Graz, Austria, argues that histology should be a key factor, whereas, Prof Sebastian Mueller, University of Heidelberg, Germany, suggests that non-invasive methods have a larger potential.

Prof Lackner recommends liver biopsy to confirm alcoholic steatohepatitis (ASH) in high-risk patients; the histological severity of ASH is a predictor of short-term mortality and infection, therefore patients with histologically confirmed ASH should be treated with steroids. Also, relying on only clinical criteria can result in a 10-50% risk of misclassification of patients with or without ASH.

Prof Lackner said: "We developed a novel non-invasive model derived from clinical and biochemical parameters for the prediction of intermediate and long-term prognosis and show that addition of histological information improves the performance of the non-invasive model."

However, Prof Mueller places an emphasis on the potential of non-invasive methods; novel elastographic techniques, such as imaging or shear wave elastography (SWE), can assess the fibrosis and patients with ALD. There are also a number of biomarkers being investigated which can assess the degree of steatosis, steatohepatitis, and iron. In the view of Prof Mueller: "Non-invasive biomarkers usually have a significantly lower sample error and are ideal for longitudinal follow-up. Liver biopsy remains an important option either to confirm ALD in relation to other potential causes or for prognosis assessment."

Both investigative methods have their limitations but the liver biopsy still remains the gold standard in the evaluation of alcoholic liver disease. The combination of invasive methods may seem favourable but when used complementary to the liver biopsy, the accuracy of diagnosis is increased, which leads to a better prognosis for the patient.

"Non-invasive biomarkers usually have a significantly lower sample error and are ideal for longitudinal follow-up. Liver biopsy remains an important option either to confirm ALD in relation to other potential causes or for prognosis assessment."

Prof Sebastian Mueller, University of Heidelberg, Germany

Alcoholic smokers at severe risk of chronic pancreatitis

> "Unfortunately, chronic pancreatitis caused by alcohol and nicotine abuse also carries a significant risk of pancreatic cancer, which is one of the deadliest cancers."
>
> *Prof Matthias Löhr, Karolinska Institutet, Stockholm, Sweden*

ALCOHOLIC patients, particularly those who smoke, could have chronic pancreatitis, especially if they present symptoms of abdominal pain and diarrhoea, and this must be remembered by the diagnosing physicians.

Prof Matthias Löhr, Karolinska Institute, Stockholm, Sweden, said: "There are many different causes of abdominal pain, including chronic pancreatitis, which is a common condition but often forgotten by both patients and physicians. I want to encourage doctors to think about the possibility of chronic pancreatitis in patients with abdominal pain and loose stools or diarrhoea - especially if alcohol and smoking are in the patient's history."

Chronic pancreatitis can be caused by excessive alcohol consumption, and smoking also exacerbates the condition. This affects approximately 1 in every 10,000 people across Europe and is more prevalent in men than women.

"Unfortunately, chronic pancreatitis caused by alcohol and nicotine abuse also carries a significant risk of pancreatic cancer, which is one of the deadliest cancers," warned Prof Löhr. "This makes it essential that we do not overlook the possibility of chronic pancreatitis when symptoms arise and that we move quickly to make a definitive diagnosis in order to treat and monitor these patients."

Diagnosis is difficult in the early stages since there must be progressive damage to the pancreas before presentation of symptoms. The first-line of investigation is an ultrasound scan of the pancreas, and then endosonography for more detailed visualisation. The use of analgesics and other medications to control pain, and enzyme replacement therapy given to aid digestion, concomitantly with alcohol and smoking cessation are essential to managing the condition.

Cell count can reduce complications after pancreaticoduodenectomy

PANCREATICODUODENECTOMY, or the Whipple procedure, does not come without complications; a simple test however, may be able to predict any possible complications after the procedure is performed. Developed by scientists in Finland, the test analyses the number of pancreatic acinar cells in the cut edge of the pancreas; the more there are, the more likely it is that complications will arise.

The Whipple procedure is the most commonly performed surgery to remove tumours from the pancreas. It can be a curative, challenging operation with a significant risk of post-operative complications, such as leaking from the pancreatic anastomosis, and mortality.

The aim of the Tampere Pancreas Group was to predict and prevent complications after the procedure, according to Dr Johanna Laukkarinen, Tampere University Hospital, Finland. This test could aid surgeons in identifying patients in whom trauma to the pancreas could be minimised.

Dr Laukkarinen said: "Our studies have shown that patients with over 40% of acinar cells in the pancreatic resection line are at high-risk of developing pancreatitis, which often precedes other post-operative complications." Dr Laukkarinen also added: "If we can prevent the initiation of this inflammatory cascade by avoiding pancreatic trauma during surgery, we may prevent the development of other complications."

As a result of this, the Finnish team have also developed a binding pancreatic anastomosis, which, in the view of Dr Laukkarinen: "Compared with the previous experiences, according to our prospective trial with 161 patients, this novel anastomosis seems to be a safe and secure technique that may decrease the rate of pancreatic leakage after this procedure."

> "If we can prevent the initiation of this inflammatory cascade by avoiding pancreatic trauma during surgery, we may prevent the development of other complications."
>
> *Dr Johanna Laukkarinen, Tampere University Hospital, Finland*

Refractory coeliac disease: new targeted therapies

SEVERE forms of refractory coeliac disease (RCD) could be treated by targeted therapies as more understanding of the pathogenesis of the condition is emerging.

Dr Georgia Malamut, Paris Descartes University, France, mentioned: "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." Treatment currently leaves sufferers with ongoing symptoms and increases patient risk of developing cancer.

RCD occurs in patients who have previously been diagnosed with coeliac disease, and those who have been engaging in a gluten-free diet for at least 12 months, yet still experience symptomatic malabsorption and severe enteropathy.

> "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."
>
> *Dr Georgia Malamut, Paris Descartes University, Paris, France*

This new research exposes two distinct forms of RCD with two different pathogenic mechanisms. The first, type 1, emulates the traditional coeliac disease and is likely to be a result of inflammation due to autoimmunity. Type 2 RCD simulates a low-grade lymphoma, and results in abnormal lymphocytes found concentrated in the lining of the intestine.

These new discoveries have enabled treatment options to evolve and thus improve clinical symptoms. RCD type 1 treatment involves steroids and immunosuppressive drugs, although, these do not reshape the pathology and often present undesirable side-effects. RCD type 2 however, is treated by more aggressive methods, such as chemotherapy, as diagnosis is poor. New investigations are underway into stem cell transplantation with chemotherapy as a combined treatment.

Dr Malamut stated: "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." She added: "In my opinion, these treatment advances cannot come soon enough."

New syndrome non-coeliac gluten sensitivity requires understanding

> "We were very interested to find that the vast majority of individuals referred to secondary care with gluten sensitivity were diagnosed with NCGS and that these people were far less likely to have nutritional deficiencies or autoimmune disorders than the patients diagnosed with coeliac disease."
>
> *Prof David Sanders, Sheffield Teaching Hospital, UK*

COELIAC disease was, until recently, the only recognised gluten-sensitive medical condition. Now, a new syndrome has been accepted: non-coeliac gluten sensitivity (NCGS).

This new condition however, has caused confusion among gastroenterologists and other medical professionals. It is problematic differentiating between this condition and coeliac disease based on symptoms alone. It is believed that NCGS is more common than coeliac disease, as a recent study from the UK indicated; out of every 100 patients with gluten sensitivity referred for specialist investigation, 10 will be diagnosed with coeliac disease and the remaining 90 will have NCGS.

Prof David Sanders from the Sheffield Teaching Hospitals in Sheffield, UK, stated: "In this study, 13% of adults screened in the general population said they had gluten sensitivity, which is a significant number of people." He added: "We were very interested to find that the vast majority of individuals referred to secondary care with gluten sensitivity were diagnosed with NCGS and that these people were far less likely to have nutritional deficiencies or autoimmune disorders than the patients diagnosed with coeliac disease."

It was suggested that blood tests and a gastroscopy with a biopsy of the small bowel should be carried out on patients presenting symptoms, in order to exclude coeliac disease. Prof Sanders however, does not believe a gluten-free diet should be prescribed immediately to those diagnosed with NCGS. He added: "Depending on how symptoms progress after the diagnosis, patients may choose to reintroduce a gluten-free diet at a later date or they may be able to gradually increase their gluten intake."

Defining the role of infliximab treatment in IBD

INFLIXIMAB treatment, used in patients with inflammatory bowel disease (IBD), has some advantages to guide dosing during optimisation of infliximab therapy, but continuous drug level monitoring is not needed to maintain this effect.

The use of monoclonal antibodies, such as infliximab, has transformed the management of individuals with IBD. However, as the immune system recognises these drugs to be foreign, not all patients respond favourably. Consequently, this is costing the healthcare system considerably as they are treating drug-resistant patients, or treating patients sub-optimally.

The aim of the TAXIT study, a prospective, randomised, controlled study, was to investigate the effects of tailored-dosing of infliximab in IBD patients treated with maintenance therapy.

Dr Niels Vande Castelle, Laboratory for Therapeutic Diagnostic Antibodies, Leuven, Belgium, said: "While we found that dosing to target levels of infliximab resulted in more efficient use of the drug in the initial treatment phase, once treatment had been optimised, dosing decisions based on drug levels or clinical symptoms produced similar clinical outcomes."

> "What this study tells us is that treat-to-target dosing of infliximab results in higher efficacy and better cost-effectiveness of the drug during the dose optimisation phase of treatment."
>
> *Dr Niels Vande Castelle, Laboratory for Therapeutic Diagnostic Antibodies, Belgium*

The study included 178 patients with Crohn's disease (CD), and 85 with ulcerative colitis (UC). Infliximab dosing was initially optimised based on precisely-measured drug levels, with the aim of achieving a trough drug level between 3 and 7 μg/ml.

During the study, patients were entered into the maintenance phase which showed no superiority of drug level-based dosing over clinically-based dosing. During the dose-optimisation phase, intensification of infliximab in CD patients with a low infliximab level resulted in better disease control, whereas dose reductions in patients with CD or UC with high drug levels resulted in a lower drug exposure and drug costs while maintaining disease control.

Dr Vande Castelle said: "What this study tells us is that treat-to-target dosing of infliximab results in higher efficacy and better cost-effectiveness of the drug during the dose optimisation phase of treatment. However, once treatment is optimised, clinicians can safely revert to clinical monitoring without compromising treatment outcomes."

Do immunosuppressants increase the risk of skin cancer? The jury is out

IMMUNOSUPPRESSANTS, which are used for treating patients with inflammatory bowel disease (IBD), may increase the chances of developing skin cancer. However, patients with IBD appear to be at an increased risk of developing cancer regardless of the treatment they are receiving.

Effective immunosuppressants include: thiopurines, azathioprine, mercaptopurine, and thioguanine, all of which can be used to maintain remission in patients with IBD. Associate Prof Tine Jess, a UEG 'Rising Star', from Statens Serum Institute, Copenhagen, Denmark, has suggested that it is biologically plausible that thiopurine-treated IBD patients may be at an increased risk of non-melanoma skin cancer.

"There is a growing body of evidence that thiopurine immunosuppressants increase the risk of non-melanoma skin cancer in IBD patients, but it's hard to determine by exactly how much because of the high background risk in these patients," said Prof Jess.

In 2010 a meta-analysis of data from over 17,000 patients with IBD confirmed that although the risk of overall cancer outside the intestines was not increased, IBD patients had a significantly increased risk of developing skin cancer.

Prof Jess said: "The importance of this meta-analysis was that it analysed data from studies conducted before, or just after, the introduction of immune-modulating treatments such as thiopurines." Prof Jess added: "It suggested that people with IBD do have relatively high rates of skin cancer regardless of treatment."

The extent of the adverse effects of immunosuppressants on these patients is still debated; however, a number of recent independent studies involving large numbers of IBD patients who received thiopurine has shown that there has been a doubling risk of non-melanoma skin cancer in these patients.

As a result of this, guidelines concerning the prevention of skin cancer in IBD patients need to be outlined, Prof Jess said: "There are currently no evidence-based guidelines for the prevention of skin cancer in IBD patients, which is something I think we need to address." However, as to whether these guidelines should apply to all IBD patients or just those receiving thiopurines is a matter of debate.

"There is a growing body of evidence that thiopurine immunosuppressants increase the risk of non-melanoma skin cancer in IBD patients, but it's hard to determine by exactly how much because of the high background risk in these patients."

Prof Tine Jess, Statens Serum Institut, Copenhagen, Denmark

TREATMENT OF HEPATIC ENCEPHALOPATHY: TARGETING THE GUT-LIVER-BRAIN AXIS

Summary of Presentations from the Norgine Sponsored Satellite Symposium, UEG Week, Berlin, Germany, 12th–16th October 2013

Chairperson

Rajiv Jalan[1]

Speakers

Agustin Albillos,[2] Flemming Bendtsen[3]

1. UCL Institute for Liver and Digestive Health, Royal Free Hospital, London, UK
2. Dept. of Gastroenterology and Hepatology, Hospital Universitario Ramón y Cajal, Universidad de Alcalá, CIBERehd, Madrid, Spain
3. Dept. of Gastroenterology, Hvidovre Hospital, University of Copenhagen, Denmark

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Introduction

Professor Rajiv Jalan

The pathogenesis of hepatic encephalopathy (HE) involves the interaction between two pathophysiological mechanisms: ammonia detoxification and inflammation. The neuropathology of HE is characterised by astrocyte dysfunction and swelling due to ammonia detoxification. The enzyme glutamine synthetase, which is located mainly in astrocytes, protects neurons by absorbing excess ammonia and glutamate, converting it to glutamine. The concentration of ammonia is increased in patients with hepatic failure when compared with healthy individuals, clearly indicating the significance of ammonia in the pathogenesis of HE, and as an important target for treatment. Bacterial translocation is a significant factor in driving the progression of cirrhosis, hepatic fibrosis, compensated and decompensated cirrhosis and the recurrence of HE (Figure 1). Bacterial translocation appears to be a key event in the transition from well-compensated to decompensated cirrhosis (or acute on chronic liver failure). This transition manifests in severe levels of HE, and probably contributes directly to the 'second hit' which is inflammation.

Gut Bacterial Translocation in Cirrhosis

Professor Agustin Albillos

Intestinal microflora and gut bacterial translocation (GBT) have been implicated in the pathogenesis of spontaneous bacterial infections and in the progression of cirrhosis. Bowel decontamination with quinolones or fluoroquinolones has been shown to improve survival in patients with decompensated cirrhosis. Non-absorbable antibiotics such as rifaximin reduce the rate of spontaneous bacterial infection, the rate of portal hypertension related complications, and improve survival.[1,2]

The basic mechanism that underlies most episodes of spontaneous bacterial infection in cirrhosis is GBT. GBT is defined as the growth of viable bacteria in a mesenteric lymph node culture. GBT is increased in experimental models of cirrhosis and in patients with cirrhosis and ascites.[3,4]

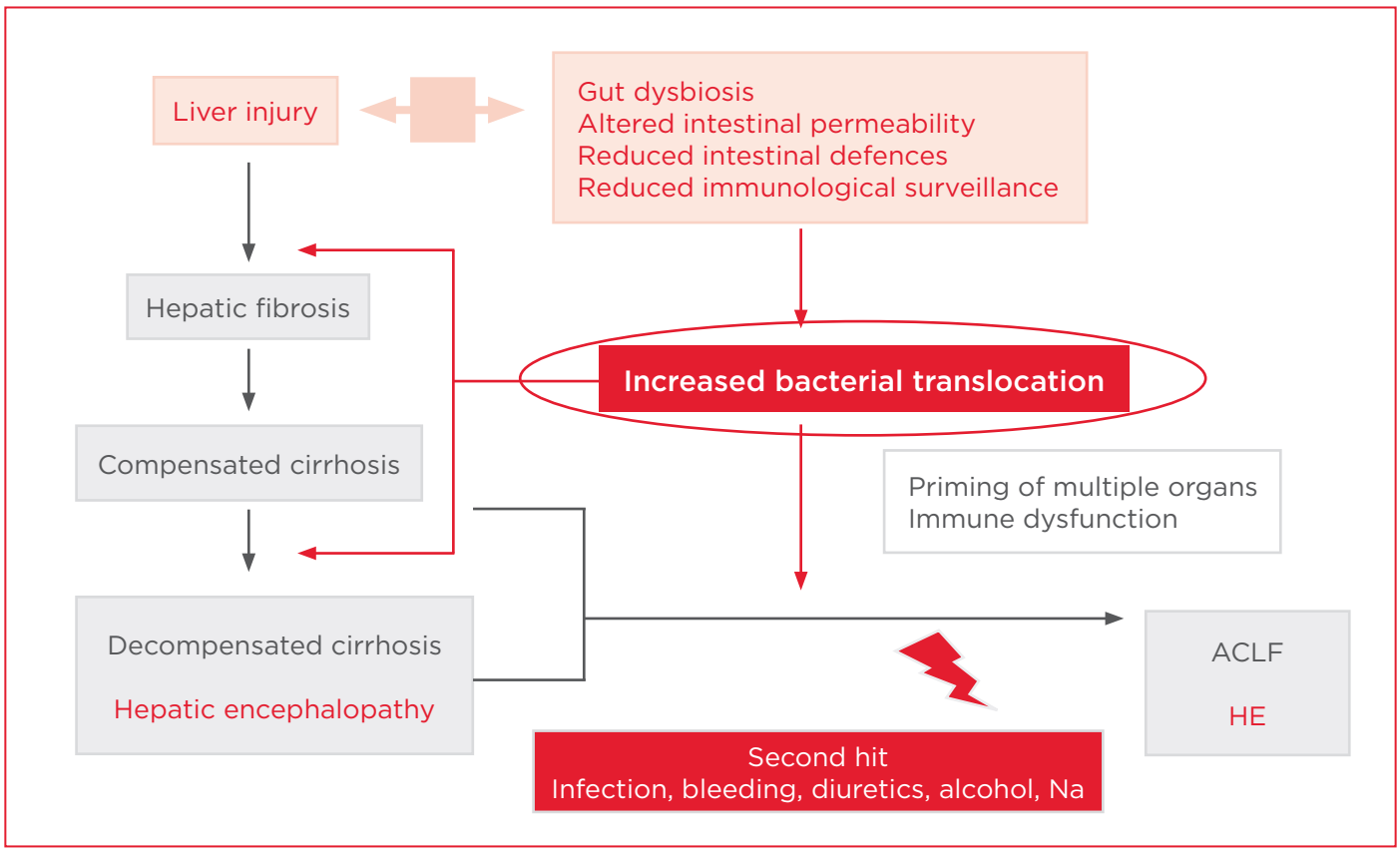

Figure 1. Inflammation in hepatic encephalopathy.

A positive mesenteric lymph node culture suggests increased passage of enteric bacteria due to increased intestinal permeability, intestinal bacterial overgrowth, or both. More importantly, it also indicates an inability of the immune system to destroy the translocated bacteria. According to the previous definition, GBT was present in about 30-40% of patients with cirrhosis and ascites and in cirrhotic rats with ascites. This demonstrates that bacterial translocation is present in advanced decompensated cirrhosis when severe liver insufficiency has already developed.

Most of the translocated bacteria belong to the common intestinal microbiota, which signifies that there is a disruption of the intestinal barrier in cirrhosis. The intestinal barrier is composed of three interrelated layers, the external composed by mucous and bacterial microflora, the epithelial cells and the sub epithelial where interactions take place between the bacteria and the immune system.[5] The integrity of the epithelial cells is the most important layer of defence against microbiota. Abnormalities in any of these levels of defence have been advocated to explain the high rate of GBT of cirrhosis. Intestinal bacterial overgrowth, increased intestinal permeability and impaired immune system response indicate changes in each of the three layers of the gut barrier in cirrhosis. In cirrhosis, there are abnormalities in the function and structure of the intestinal mucosa, involving tight junction proteins, which lead to increased permeability of macromolecules.[3] There are also qualitative (dysbiosis) and quantitative changes in gut microbiota that indicate intestinal overgrowth, which is associated with most episodes of bacterial translocation.[3] This is mainly attributed to the presence of intestinal hypomotility in cirrhosis, although impaired immunity can also contribute. However, other elements are necessary for GBT to develop; these are predominantly linked to the hepatic insufficiency that is found in cirrhosis. The exact mechanism is unclear, but it is possibly related to impaired immune function considering the role of the liver in innate immune function. There might also be contribution of the neuroendocrine abnormalities present in liver cirrhosis, specifically sympathetic nervous system hyperactivity and changes in bile flow and composition. Therefore, GBT in liver cirrhosis is

the result of damage at different levels of the intestinal barrier, i.e. changes in microbiota, changes in the integrity of the epithelium and impaired immunity (Figure 2).

In the absence of overt infection, GBT contributes to cirrhosis progression by inducing an activation of the immune system at the systemic level.[2] Systemic inflammation results from the production and release of pathogen-associated molecular patterns that activate specific receptors on the surface of immune cells. This results in the production of proinflammatory lymphokines and monokines, and circulating immune system cells in cirrhosis produce proinflammatory cytokines. This mechanism modulates the clinical expression of cirrhosis, for example the modulation of the activity of astrocytes leading to the neurological changes of cirrhosis or the regulation of vascular tone. Persistent activation of immune cells worsens the immunodeficiency of cirrhosis because it leads to the exhaustion and death of the cells (Figure 3). This situation can be reversed by reducing the enteric bacterial load with non-absorbable or poorly absorbable antibiotics.[6] This was shown in a study where bowel decontamination with antibiotics improved the dendritic cell function of the intestinal lamina propria of cirrhotic rats with bacterial translocation.

Multiple intestinal damage in cirrhosis involves different potential therapeutic targets. These include bile acids, farnesoid X receptor (FXR) agonists for impaired bile flow or composition, beta-blockers for intestinal hypomotility, antioxidants for inflammation oxidative stress and antibiotics, and probiotics for microbiota. The most effective treatment is controlling the microbiota with non-absorbable antibiotics to prevent spontaneous bacterial infection. The use of other specific

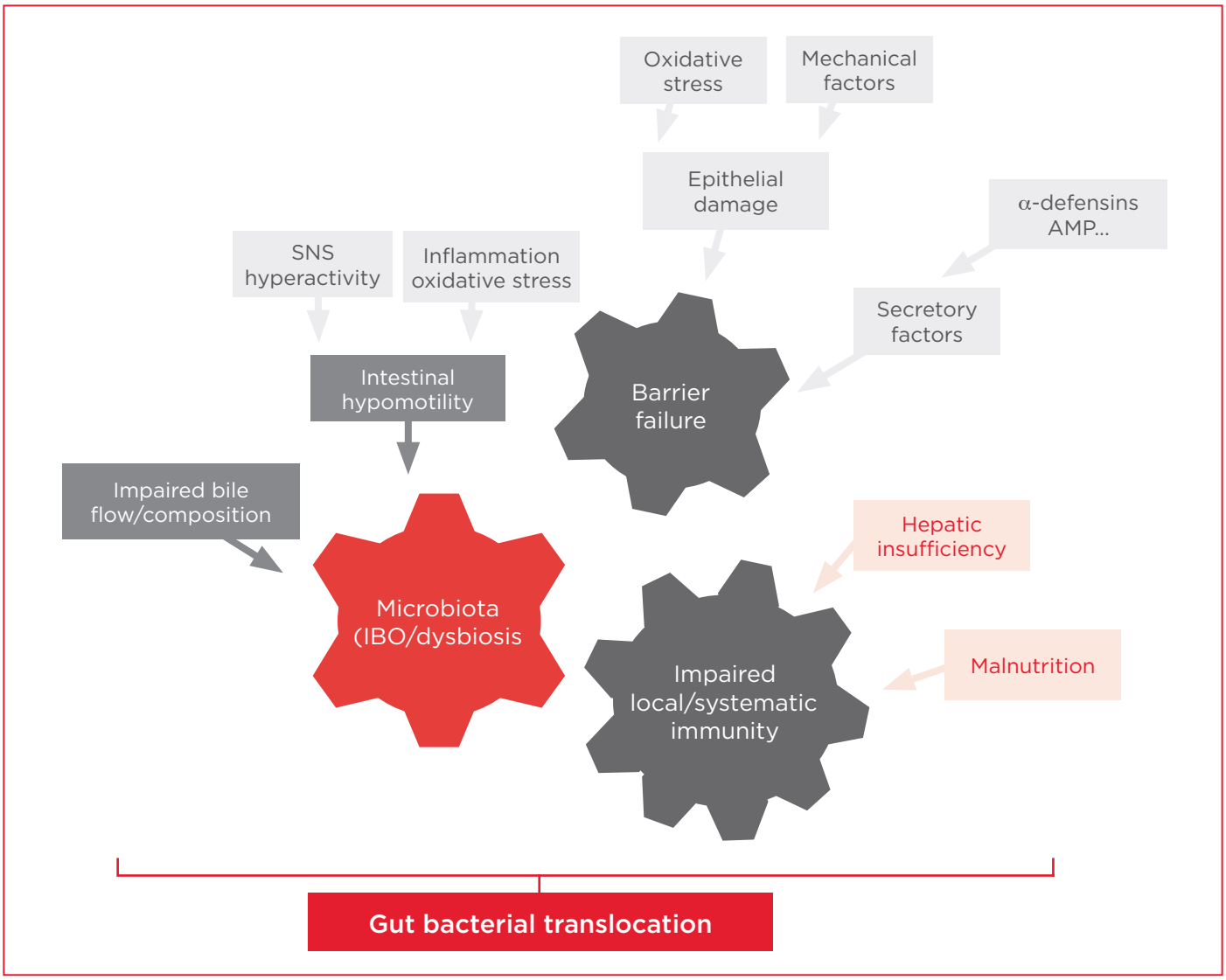

Figure 2. Mechanisms of gut bacterial translocation in advanced cirrhosis.

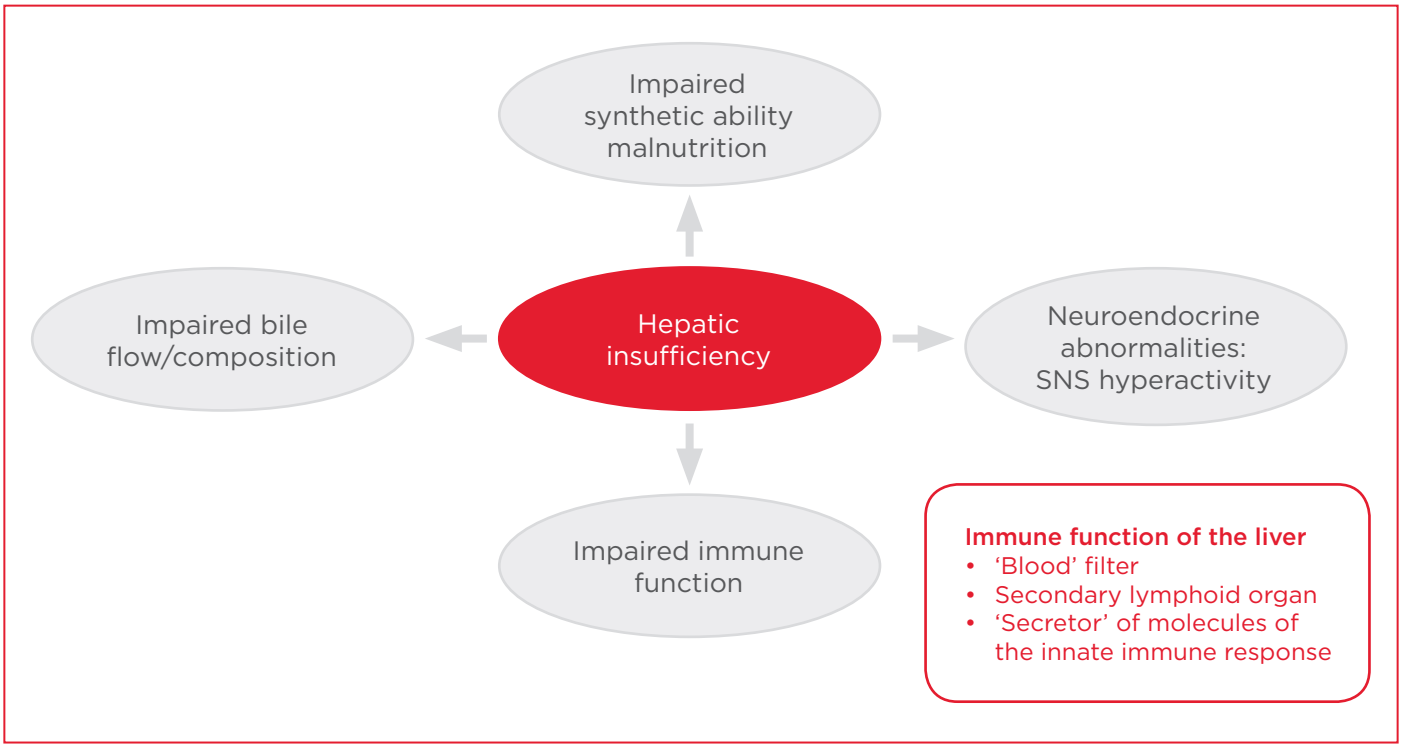

Figure 3. The consequences of hepatic insufficiency that contribute to GBT in cirrhosis.

targeted agents (FXR agonists, antioxidants and probiotics) has only been studied in experimental settings; therefore, efficacy data in patients are not available. However, the use of beta-blockers in cirrhotic patients has been shown to be beneficial by reducing portal pressure and GBT.[7] This was demonstrated in cirrhotic rats; propranolol was shown to accelerate intestinal transit and lower intestinal bacterial overgrowth and GBT to mesenteric lymph nodes.

In summary, GBT in cirrhosis is the pathophysiological hallmark of spontaneous bacterial infections. GBT contributes to further decompensation in already decompensated cirrhosis by driving a persistent activation of the inflammatory immune system and exacerbating immunodeficiency. As the pathogenesis of GBT in cirrhosis involves damage at different levels of the intestinal barrier, there are multiple potential targets for the control of GBT. Although most targets have only been tested in an experimental setting, it has been shown that bowel decontamination improves outcomes in patients with decompensated cirrhosis. Furthermore, beta-blockers improve survival by reducing the variceal bleeding risk and bacterial translocation.

Clinical Consequences of Bacterial Translocation – Does Gut Decontamination Improve Outcome?

Professor Flemming Bendtsen

Bacterial translocation is associated with cirrhosis and portal hypertension and contributes to splanchnic vasodilation and systemic vasodilation. Therefore, clinicians should focus on bacterial translocation in patients with ascites and decompensated liver disease. As a consequence of portal hypertension and possibly GBT, patients may develop an increased hepatic venous pressure gradient (HVPG) resulting in the formation of oesophageal varices. Furthermore, systemic inflammatory response leads to disease progression, with an associated increased risk of infection. Structural and functional changes in the gut mucosa, bacterial overgrowth in the small intestine, impairment of defence mechanisms, and decreased gut motility can all lead to bacterial translocation.

Bacterial decontamination is believed to modify the risk of complications of portal hypertension. There are no large clinical trials that evaluate clinical endpoints such as death, development of variceal bleeding, hepatorenal syndrome, and

other complications of cirrhosis. However, there are trials that evaluate surrogate markers such as the effect on haemodynamics and inflammation, vasoactive hormones, and inflammatory markers. Albillos et al.[2] evaluated lipopolysaccharide binding protein (LBP) levels in cirrhotic patients with marked immune and haemodynamic derangement. Patients were randomised to either norfloxacin (which targets most of the Gram-negative bacteria in the intestine) or to placebo. A further sub-division of patients was made into those that had signs of inflammation with an increased LBP at baseline, and those with normal LBP. The patients with increased LBP had more severe signs of derangement in their haemodynamic evaluations; these included decreased blood pressure (BP) and higher pulse rate leading to a hyperdynamic circulation with increased cardiac output. Hepatic venous catheterisation was performed to measure HVPG. In patients with a high LBP randomised to norfloxacin, 4 weeks' treatment had a beneficial effect on BP and systemic vascular resistance when compared with baseline measurements. However, no effect was seen on HVGP in this study. Norfloxacin demonstrated a clear effect on LBP (a marker of bacterial translocation) whereas no effect was seen with placebo (Figure 4).

The results of this study concur with those of a randomised crossover trial[8] in which patients with cirrhosis were randomised to placebo or norfloxacin for 28 days, and then crossed over to the treatment not previously received. A clear effect was seen on systemic vascular resistance, but no effect was seen on HVPG in patients receiving norfloxacin. Furthermore, the study evaluated blood flow and found that BP increased and systemic vascular resistance increased in patients receiving norfloxacin. These studies demonstrate that treatment with norfloxacin generates a significant beneficial change in systemic haemodynamic parameters, but not in splanchnic haemodynamic parameters.

Although the non-absorbable antibiotic norfloxacin does not appear to have an effect on splanchnic haemodynamics, recent studies indicate that rifaximin might reduce HVPG.[9] Patients were given rifaximin 1200 mg daily for 29 days, HVPG was measured at baseline and at day 29. The results showed a decrease in HVPG. However, this study was uncontrolled and it is unclear whether this limitation skewed the results, or whether there is a true treatment effect. Unlike norfloxacin, rifaximin has a broader microbial spectrum and has an effect on Gram-positive bacteria.

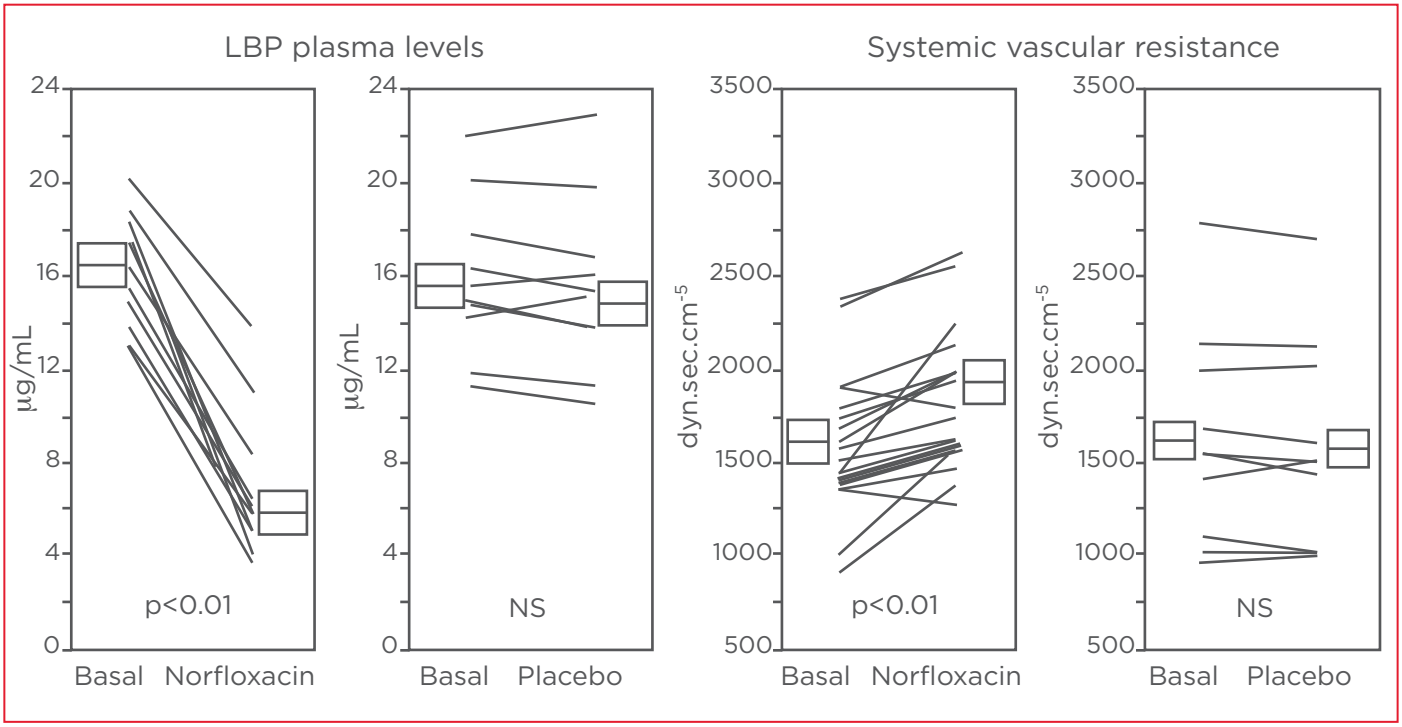

Figure 4. The effect of 4 weeks' treatment with norfloxacin on LBP and systemic vascular resistance in patients with signs of bacterial translocation (high LBP).
Albillos A et al.[2]

Table 1. Systemic haemodynamics, endogenous vasoactive systems, renal function, body weight, and inflammatory markers pre and post treatment with rifaximin.

	Baseline	Rifaximin	P
Systemic haemodynamics and endogenous vasoactive systems			
Mean arterial pressure, mm Hg	90 (81.6–101.6)	92 (86.3–106.6)	0.05
Cardiac output, L/min	6.01 (4.77–8.76)	5.76 (4.1–8.04)	0.02
Systemic vascular resistance, dynes * sec * cm-5	1500 (960–1815)	1619 (1163–2243	0.01
Plasma renin activity, ng/mL/h	6.85 (1.17–16.98)	5.59 (1.06–14.6)	0.02
Plasma aldosterone level, pg/mL	637.2 (311–1323)	495.2 (231.6–1245)	0.06
Renal function and body weight			
Serum creatinine level, mg/dL	0.9 (0.8–1.2)	0.9 (0.8–1.1)	0.6
Serum urea level, mg/dL	34 (18–50)	33 (20–46)	0.2
Glomerular filtration rate, mL/min	65 (40–84)	66 (39–91)	0.006
Urinary sodium level, mmol/d	47.5 (22–100)	48.6 (25.4–106)	0.03
Weight, kg	72.8 (60.2–81.5)	72 (59.6–81)	0.1
Circulating endotoxin and cytokine concentrations			
Plasma endotoxin, EU/mL	1.07 (0.65–10)	0.56 (0.37–5.23)	0.005
Serum interleukin-6, pg/mL	18.82 (3.97–54.85)	12.49 (1.87–30.11)	0.01
Serum tumour necrosis factor-, pg/mL	5.51 (3.84–10.47)	3.78 (2.34–7.26)	0.02

Note: Data are expressed as the median and range.
Kalambokis GN et al.[10]

In an uncontrolled study, rifaximin has been shown to improve systemic haemodynamics and renal function in patients with alcohol-related cirrhosis and ascites.[10] In an open label study, 15 patients with ascites and Child-Pugh B or C cirrhosis received 1200 mg of rifaximin daily for 4 weeks. Haemodynamic parameters, renal function tests and measurement of inflammation markers were measured at baseline and at day 28. The results showed that rifaximin had a positive effect on the systemic haemodynamic parameters (Table 1). This study indicates that rifaximin has an effect on surrogate markers by decreases in cytokine levels, (which are the signals of bacterial translocation), and on haemodynamics.

None of the studies of the effects of gut decontamination in cirrhosis are double-blind or placebo controlled. However, it appears from the evidence available that gut decontamination prevents relapse of HE, improves systemic haemodynamics by an increase in BP and a decrease in cardiac output, decreases immune activation, and may improve renal function. The effect of gut decontamination on splanchnic haemodynamics is yet to be proven.

A randomised, double-blind, placebo controlled study is in progress. This study is investigating intestinal decontamination with rifaximin in cirrhotic patients with ascites, and assessing the effects on haemodynamic and inflammatory factors.[11] The aim of the study is to stop progression of liver disease by inhibiting bacterial translocation via bowel decontamination. The outcome measures are to reduce portal hypertension, diminish vasodilation, increase glomerular filtration rate, normalise inflammation and decrease risk of infection (Figure 5).

There is a need for a large scale, randomised, double-blind, placebo controlled study, addressing gut decontamination in decompensated cirrhosis. The clinical endpoints should include mortality, the risks of variceal bleeding, infections (especially spontaneous bacterial peritonitis), and hepatorenal syndrome.

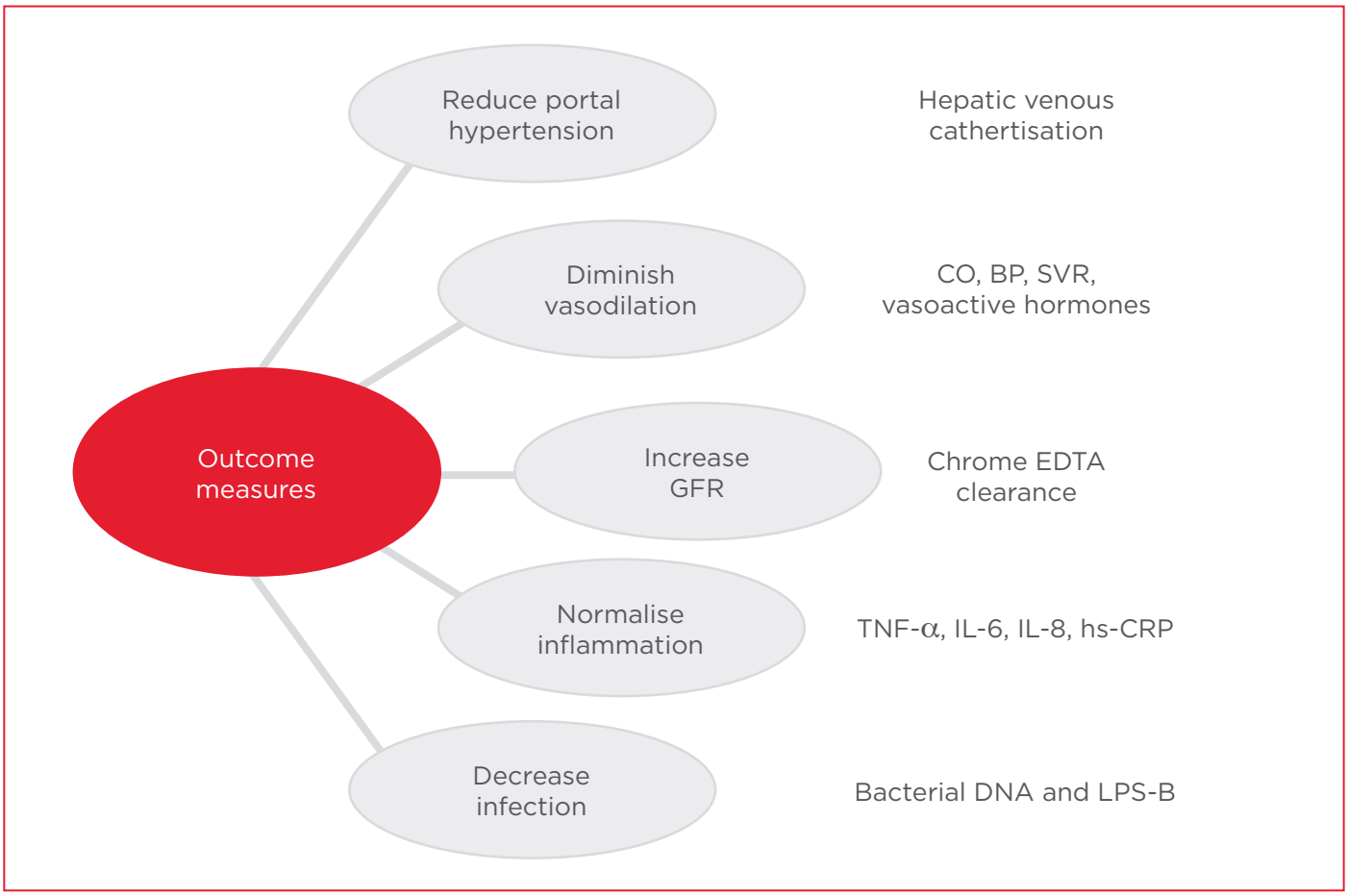

Figure 5. Outcome measures in an ongoing study of rifaximin in cirrhotic patients with ascites.

Treatment of Hepatic Encephalopathy: Targeting the Gut-Liver-Brain Axis. Gut Decontamination and HE. The More Things Change, the More They Remain the Same

Professor Rajiv Jalan

There have been significant advances in the treatment of HE, predominantly involving targeting the gut-liver-brain axis and gut decontamination. The current treatment concepts are illustrated by the following case study.

A 53 year-old male Afro-Caribbean lawyer was transferred from a neurology hospital where he had been an inpatient for 2 months. The patient had a history of haematemesis and melaena, spastic paraparesis, and a previous history of alcohol abuse and mildly abnormal liver function tests. On admission to the Intensive Care Unit (ICU) the patient had fluctuating levels of consciousness with a Glasgow Coma Scale (GCS) of 4-5. Immediate management included resuscitation, transfusion and an upper gastrointestinal endoscopy. This showed Grade 3 oesophageal varices which were treated with banding and achieved good control of the bleeding. The patient was treated with terlipressin for 3 days, antibiotics, thiamine and lactulose. The initial diagnosis was cirrhosis and oesophageal varices (a complication of the disease). The patient had been previously fit and well, and had a flourishing law practice until 2006. He retired prematurely in July 2009 due to progressive leg weakness that started in 2006, and became wheelchair bound in 2011. The patient had undergone extensive investigations at the specialist neurology hospital and a working diagnosis of spastic paraplegia of unknown origin was made.

Following admission to the ICU, neurological examination on day 4 revealed that he was still unresponsive with a GCS of 4-5, had Grade 3-4 HE and had very little power in both legs. Abdominal examination showed mild

hepatosplenomegaly, no ascites and no peripheral stigmata of liver disease. Despite the very large 'hit' the patient had experienced, his chest was clear and lung function was normal, heart rate was 78 beats/minute, BP 143/78 mmHg, and kidney function was acceptable (creatinine 78 μmol/L). Liver investigations showed mildly elevated bilirubin (37 μm/L which equates to 2 mg/dL), and his creatinine was normal (65 μm/L which equates to between 0.7 and 0.8 mg/dL). The model for end-stage liver disease (MELD) score was 10; indicating very mild early chronic liver disease with portal hypertension. All the viral serology results were negative, except Hep B sAG and Hep B eAg (due to previous exposure to Hepatitis B), but HBV was negative. These findings suggested underlying alcoholic cirrhosis which was well compensated. Liver ultrasound demonstrated a normal liver, splenomegaly (14.5 cm) and a trace of pelvic ascites. MRI of the liver showed no evidence of chronic liver disease; the biliary system was normal and a normal total liver volume of 1,382 mL. Transjugular liver biopsy demonstrated evidence of alcoholic cirrhosis. Consequently, a diagnosis of well compensated alcoholic cirrhosis with portal hypertension was made. The patient had a neurological deficit; he was comatose and had spastic paraplegia which was initially thought to be unrelated. On day 5, the results of an ammonia test were 145 μmol/L (normal is <40), this indicated that the patient's condition was due to HE. Therefore, lactulose was increased to 15 mL three times a day (tds) and treatment with rifaximin 550 mg twice a day (bd) was commenced. GCS remained at 4–5 for a further 5 days and the patient developed diarrhoea (culture and sensitivity was negative) which led to rifaximin and lactulose being stopped.

A CT scan of the abdomen showed a large spontaneous portacaval shunt emanating from the left renal vein. Brain MRI showed an increased pallidal hyperintensity on T1 imaging, and MR spectroscopy showed an elevated glutamine level. The patient showed evidence of brain dysfunction with hyperammonemia, increased brain glutamine, spastic paraparesis, and pallidal hyperintensity indicating that the syndrome may be a result of brain dysfunction precipitated by cirrhosis. A diagnosis of severe HE was made and embolisation of the patient's shunt was considered. Embolisation is a useful treatment for HE and a MELD score of ≤11 predicts a good response to therapy.[12] However, this patient had portal hypertension and a recent variceal bleed and if the shunt were to be blocked, the portal hypertension would become worse. Consequently, the treatment strategy was to insert a small diameter Transjugular Intrahepatic PortoSystemic Shunt (TIPSS) and through the TIPSS, embolise the shunt and control the shunt. The patient remained in ICU and gradually woke up over the next 6 days.

On the ward between days 18 and 28 it became apparent that the patient had persistent Grade 2 HE and remained significantly hyperammonemic (75–90 μmol/L). Treatment with lactulose 15 mL tds and rifaximin 550 mg bd was restarted. Recommencement of rifaximin was in line with findings by Bass et al.[13] that showed that patients discharged from hospital who had been treated with rifaximin had fewer HE relapses and hospital admissions. The study (Figure 6) found a 50% relative risk reduction and a 9% absolute risk reduction in patients treated with rifaximin (hazard ratio 0.50 [95% CI, 0.29–0.87] p=0.01).

The patient was discharged from hospital to a rehabilitation centre on day 42. His ammonia levels had improved (35–42 μmol/L), neurologically the GCS was 15, and he remained mildly encephalopathic (Grade 1). The patient was followed-up closely; the treatment strategy was to continue lactulose and rifaximin, and if no improvement was seen liver transplantation would be considered. Weissenborn et al.[14] showed that patients who have large portacaval shunts can develop HE and hepatic myelopathy, which may be reversible with liver transplantation. In this patient, liver transplantation was indicated for hepatic myelopathy because it was thought that the spastic paraparesis may be related to HE.

On review 8 months later, the patient had no further hospital admissions for HE and continued on treatment with lactulose and rifaximin, which he tolerated quite well. Ammonia levels had varied between 30 and 40 μmol/L, and there had been a gradual improvement in the power of both lower limbs with physiotherapy, nutritional support and drug treatment. The patient had responded to multiple level interventions, not only from a neurological state but from spastic paraparesis as well. The final diagnosis was alcoholic cirrhosis with portal hypertension, HE and hepatic myelopathy.

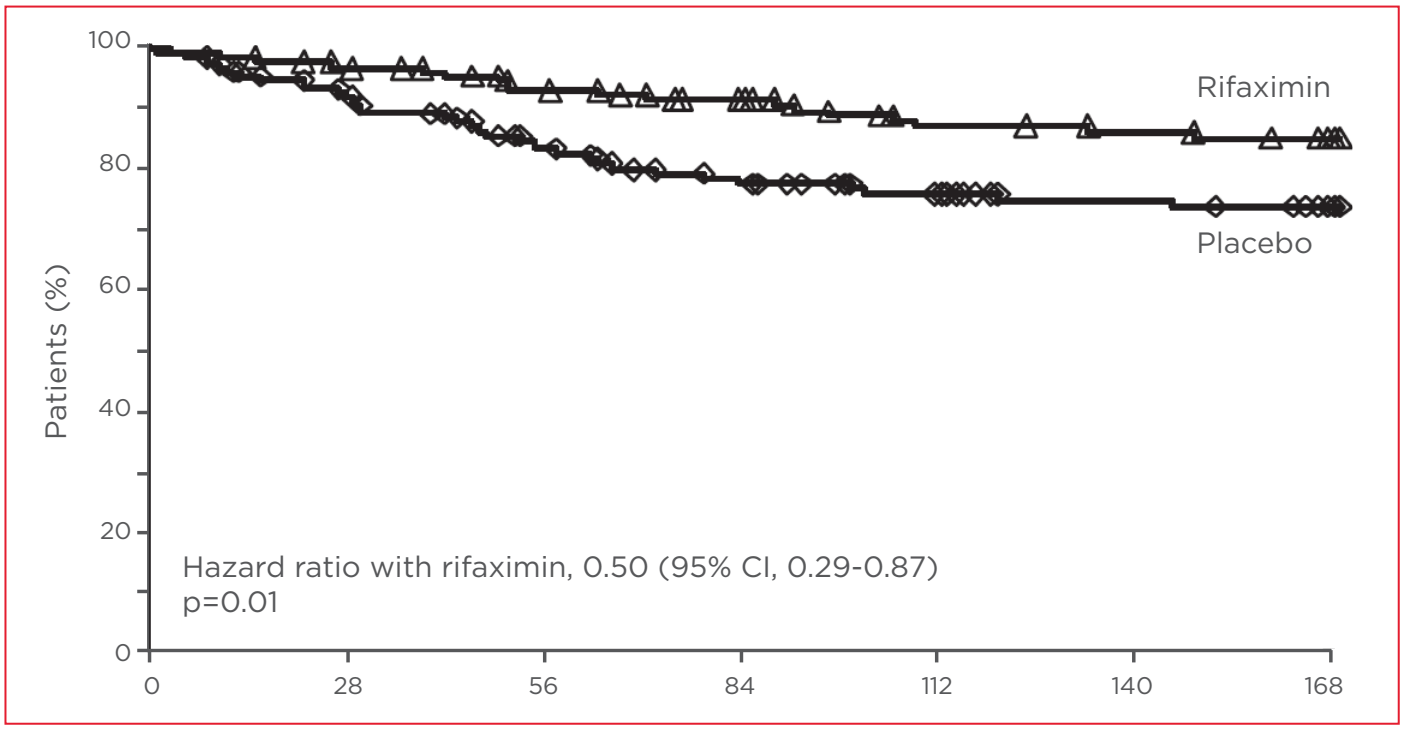

Figure 6. Time to first HE-related hospitalisation (secondary endpoint).
Hazard ratio with rifaximin, 0.50 (95% CI, 0.29-0.87) p=0.01.
Bass et al.[13]

Knowledge of the pathogenesis of cirrhosis may not have changed. The role of the gut was first described in 1893 by Necki et al.[15-17] who made the following observations: ammonia was coming from the gut and portal ammonia was greater than arterial ammonia (the current treatment for this is lactulose and rifaximin); ammonia concentration is increased in the muscle and kidney (the proposed treatment today is ornithine phenylacetate); ammonia concentration is raised in the gastric mucosa even in a fasting state (now there may be a role for *H. Pylori* eradication therapy); ammonia was raised in the kidney of the portacaval shunted dog, and urinary ammonia excretion increased after a meat-meal or ammonia administration (the current treatments are volume expansion, ornithine phenylacetate, gut lavage, and rifaximin). These observations raise the question of how far we have actually progressed; the gut-liver axis was really described more than 120 years ago.

Panel Discussion: The Role of Non-Absorbed Antibiotics in Gut Decontamination

GBT plays an important role in HE. Key mediators in GBT that drive this include the presence of bacteria in the circulation or tissues, as well as bacterial products that stimulate an inflammatory reaction (e.g. bacterial DNA). Furthermore, it is not the response itself that should be targeted but the location where it originated – the gut-liver axis.

There is a need for more controlled trials on GBT and gut microbiota, with patients with clear signs of bacterial translocation as the focus. Parameters that prove that bacterial translocation is present (e.g. an increased LBP or a high level of cytokines) should be measured. Targeting GBT requires the use of a very broad spectrum, non-absorbable antibiotic, such as rifaximin, which should be tested in this context. Rifaximin has shown efficacy in bowel decontamination with very few side-effects.

A clear target for gut decontamination is a decompensated cirrhotic patient with ascites who has signs of inflammation that are attributable to GBT. In this group of patients, gut decontamination is likely to improve survival. It has been shown that in spontaneous bacterial translocation, norfloxacin would

not be sufficient to eradicate the bacteria and overgrowth in the intestine. Consequently, a drug is required to target both Gram-positive and Gram-negative bacteria: rifaximin has a non-selective, broad antibiotic spectrum and acts on both Gram-positive and Gram-negative bacteria.

The case study demonstrated that the pathology of hepatic myelopathy is a loss of the anterior horn cells; producing a very severe form of HE. There are two types of hepatic myelopathy: a reversible form, and an irreversible form. It is difficult to distinguish the types of hepatic myelopathy in a patient, but both types result from large, long-standing porto-systemic shunt. Liver transplantation is a treatment option for these patients but not all respond and the type of hepatic myelopathy present in responders is unknown.

In the treatment of HE, liver transplantation may not be the first treatment choice – particularly if the chance of recovery is not evident. There are several different treatment options and indicators that can be considered. In comatose patients with liver disease who have clinical signs of HE, ammonia is a useful indicator of the severity of encephalopathy. Accurate measurement can indicate a target for intervention, and in the context of acute liver failure, ammonia provides a measurement to follow as an endpoint to intervention. However, the measurement of ammonia is difficult and must be performed using a validated technique.

The insertion of TIPSS in patients with long-term HE has been suggested to be contraindicated. The case study patient illustrated a treatment strategy when limited options are available. The patient had experienced a variceal bleed and there was a high chance of re-bleeding if the spontaneous large portosystemic shunt was occluded for the treatment of HE. Therefore, a small 8 mm shunt was inserted that could be stretched if the patient bled, providing an opportunity to rescue the patient. Small shunts are at risk of closure therefore a low level of anticoagulation is required.

Faecal transplantation is a therapeutic option that has been suggested in patients with *Clostridium difficile* infection. However, in patients who are immunosuppressed due to cirrhosis, this may not prevent bacterial overgrowth in the small intestine, and as a result is unlikely to benefit many patients.

Clinical experience demonstrates the important role of non-absorbable antibiotics in gut decontamination in patients with HE.

REFERENCES

1. Leise MD et al. Impact of rifaximin treatment on survival in patients with end-stage liver disease. Hepatology. 2010;52:331A.

2. Albillos A et al. Increased lipopolysaccharide binding protein in cirrhotic patients with marked immune and hemodynamic derangement. Hepatology. 2003;37:208-17.

3. Pérez-Páramo M et al. Effect of propranolol on the factors promoting bacterial translocation in cirrhotic rats with ascites. Hepatology. 2000;31:43-8.

4. Cirera I et al. Bacterial translocation of enteric organisms in patients with cirrhosis. J Hepatol. 2001;34:32-7.

5. Hooper LV et al. Interactions between the microbiota and the immune system. Science. 2012;336:1268-73.

6. Muñoz L et al. Interaction between intestinal dendritic cells and bacteria translocated from the gut in rats with cirrhosis. Hepatology. 2012;56:1861-9.

7. Krag A et al. The window hypothesis: haemodynamic and non-haemodynamic effects of β-blockers improve survival of patients with cirrhosis during a window in the disease. Gut. 2012;61:967-9.

8. Rasaratnam B et al. The effect of selective intestinal decontamination on the hyperdynamic circulatory state in cirrhosis: a randomized trial. Ann Intern Med. 2003;139(3):186-193.

9. Vlachogiannakos J, et al. Intestinal decontamination improves liver haemodynamics in patients with alcohol-reduced decompensated cirrhosis. Aliment Pharmacol Ther. 2009;29(9):992-9.

10. Kalambokis GN et al. Rifaximin improves systemic hemodynamics and renal function in patients with alcohol-related cirrhosis and ascites. Clin Gastroenterol Hepatol. 2012;10(7):815.

11. ClinicalTrials.gov Identifier: NCT01769040

12. Laleman W. et al. Embolization of large spontaneous portosystemic shunts for refractory hepatic encephalopathy: a multicenter survey on safety and efficacy. Hepatology.2013;57(6):2448-57.

13. Bass NM et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med. 2010;362:1071–81.

14. Weissenborn K et al. Liver transplantation improves hepatic myelopathy: evidence by three cases. Gastroenterology. 2003;124(2):346-51.

15. Hahn M et al. Die Eck'sche fistel zwischen der unteren hohlvene und der pfortader und ihre folgen fur den organismus. Arch Exp Pathol Pharm. 1893;32:161-210.

16. Nencki et al. Ueber den ammoniakgehalt des blutes under der organe und die harnstoffbildung bei den saugethieren. Archiv Exp Pathologie Pharm. 1896;37:26-51.

17. Translated in: Shawcross D et al. Ammonia and hepatic encephalopathy: the more things change, the more they remain the same. Metab Brain Dis. 2005;20(3):169-79.

STATE-OF-THE-ART TREATMENT OF IRRITABLE BOWEL SYNDROME: RECENT ADVANCES AND EMERGING THERAPEUTIC ALTERNATIVES

Magnus Simrén

Consultant, Department of Internal Medicine, Sahlgrenska University Hospital, Göteborg, Sweden

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ABSTRACT

Irritable bowel syndrome (IBS) is a highly prevalent functional disorder characterised by chronic and recurrent abdominal pain and altered bowel habit. Numerous pharmacological and nonpharmacological treatment options have proven to have some benefit in the condition, and a multidisciplinary approach should ensure that treatment is tailored to the individual. Recently, an enhanced understanding of the pathophysiological processes underlying the condition has led to the development of new therapies, including prokinetic agents targeting serotonin (5-HT) pathways, and pro-secretory agents. Many are still at an early stage of clinical development, however, some have demonstrated improved outcomes in clinical trials and have gained regulatory approval. Lubiprostone, a calcium channel activator and linaclotide, a novel secretagogue that activates the guanylate cyclase C receptor, have demonstrated improvement of abdominal pain as well as improved bowel function in patients with IBS with constipation (IBS-C) in a series of randomised, placebo-controlled studies.

Keywords: Irritable bowel syndrome, constipation, linaclotide.

INTRODUCTION

Irritable bowel syndrome (IBS) is the one of the most common disorders in modern medicine. Its prevalence varies between countries, and depends on the criteria used to define it, but global prevalence has been estimated at around 15%; 9% when criteria include patients with persistent symptoms for at least 12 months.[1] IBS predominantly affects women[1] and imposes a substantial burden on healthcare systems, with reduced health-related quality of life (HR-QoL), repeated medical care visits and high costs, as well as indirect costs arising from reduced work productivity.[2,3] IBS is a functional bowel disorder characterised by intermittent episodes of abdominal pain or discomfort and altered bowel habit (diarrhoea, constipation, or alternating hard and loose stools),[4] which according to the Rome III diagnostic criteria, should be interrelated (Table 1).[5] IBS can be subtyped based on the predominant bowel habit into IBS with constipation (IBS-C), IBS with diarrhoea (IBS-D), mixed IBS (IBS-M), and unsubtyped IBS (IBS-U).[6] Besides abdominal pain or discomfort and abnormal bowel habit, patients with IBS often complain of other gastrointestinal (GI) symptoms, such as abdominal bloating, visible abdominal distention, straining, urgency, and incomplete evacuation, as well as symptoms emanating from the upper GI tract, other somatic symptoms, and psychological comorbid symptoms.[5]

The treatment of IBS requires a structured approach, accounting for both doctor and patient preferences. Given the fact that response to placebo in clinical trials of IBS is strong,[7] a good, patient-doctor relationship is of pivotal importance, with patient reassurance and education being central to management of the condition. Treatment options for IBS include pharmacological and nonpharmacological interventions and are summarised in the paper by Halland and Talley.[8] However, the development of effective drugs has been hindered by the

Table 1. ROME III diagnostic criteria and subtypes for irritable bowel syndrome.

Diagnostic criteria	IBS subtypes
Recurrent abdominal pain or discomfort for at least 3 days within the last 3 months in association with two or more of the following: • Improvement with defecation • Onset associated with a change in stool frequency • Onset associated with a change in stool form (appearance)	• IBS with constipation when at least 25% of stools are hard and fewer than 25% are loose or watery • IBS with diarrhoea when at least 25% of stools are loose or watery and fewer than 25% are hard • IBS mixed type when at least 25% of stools are loose or watery and at least 25% are hard • IBS un-subtyped when changes in stool consistency do not fit any of the previous subtypes

Longstreth et al.[5]

complex pathophysiology of the condition. IBS is a functional disorder and as such its aetiology cannot be attributed to any underlying specific disease process or structural abnormality. However, it may be associated with abnormal GI motility, visceral hypersensitivity, low-grade gut inflammation, previous intestinal infections, changes in microflora, food hypersensitivity, and psychosocial dysfunction.[9] Recent advances in the understanding of the pathogenesis of IBS have led to the development of several promising pharmaceutical agents.[10] This article aims to review the current treatment options in IBS, with a specific focus on recent advances and emerging therapeutic alternatives.

NON-PHARMACEUTICAL TREATMENT APPROACHES TO IBS

The majority of patients with IBS report that their GI symptoms worsen in response to food intake, in particular foods rich in carbohydrates and fats.[11,12] Up to half of all IBS patients have also reported intolerance to histamine-releasing food items such as milk, red wine and pork and foods rich in biogenic amines such as wine, salami, and cheese.[12] Dietary advice is frequently sought by IBS patients,[13] and represents a cost-effective therapeutic approach. Although limited clinical evidence exists in support of dietary modification, restricting rapidly fermentable, short-chain carbohydrates (FODMAPs) has proven effective in subgroups of IBS patients.[14-16] Fibre supplementation is a widely used treatment approach in IBS-C but clinical evidence in support of its use is weak.[17,18] Soluble fibre (such as psyllium) has proven more beneficial than insoluble fibre (bran).[19]

Other lifestyle interventions may be useful in the management of IBS. A randomised clinical study showed that physical activity improves GI symptoms in IBS.[20] Psychological treatment approaches may also be beneficial, and numerous approaches, including cognitive behavioural therapy (CBT), dynamic psychotherapy, biofeedback, hypnotherapy, and relaxation therapy have been studied.[21] The availability, duration, cost, and patient reluctance have limited such interventions but a growing body of evidence supports the fact that such interventions may bring about clinically meaningful improvements in symptoms and QoL, particularly in patients with low-to-moderate QoL at baseline.[22-24] In order to increase the availability of such therapies, self-administered, internet and group-based CBT are promising options.[25-27] Gut directed hypnotherapy may provide long-term benefits in terms of symptom relief and reduced medication usage.[28] A report of two recent randomised, controlled studies concluded that the treatment is effective for patients with refractory IBS, but treatment effectiveness is lower when administered outside specialist research centres.[29]

SYMPTOM-SPECIFIC TREATMENT OF IBS

Treatment directed towards specific symptoms of IBS form the backbone of IBS therapy. Osmotic laxatives such as polyethylene glycol have demonstrated efficacy in providing relief from constipation.[30] Diarrhoea may be treated

successfully with loperamide (see below), but has also been associated with bile acid malabsorption in up to one-third of patients with IBS-D; these patients respond well to the bile acid agent cholestyramine.[31,32] In terms of abdominal pain, the use of antispasmodics including hyoscine, peppermint oil, mebeverine, otilonium bromide, pinaverium bromide, and cimetropium bromide is supported by clinical data.[16,17,24] Moreover, several studies have demonstrated that antidepressants are effective in the treatment of IBS symptoms in general, and pain in particular.[20] The α2δ ligands gabapentin and pregabalin are beneficial to some IBS patients with severe abdominal pain and anxiety.[33] However, these approaches target the patient's individual symptoms at the time of the acute episode[4,34,35] and are associated with varied efficacy and poor patient satisfaction.[36]

AGENTS TARGETING PATHOPHYSIOLOGICAL PROCESSES IN IBS

Several mediators and receptors involved in IBS-related abdominal pain have been identified, including serotonin (5-hydroxytryptamine [5-HT]), tachykinins, cholecystokinin (CCK), and nerve growth factor (NGF). Their corresponding receptor antagonists have been investigated in clinical trials. However, not all have fulfilled their promise as therapeutic targets and several clinical studies have not met their primary endpoints.[37]

Opioid Receptors

Endogenous opioids regulate nervous visceral sensitivity as well as visceral motor function. Loperamide, a μ-opioid-receptor agonist, which decreases GI motility, is the first choice treatment for patients with IBS-D,[38] and others are in clinical development. In a Phase II study of IBS-D patients, the μ-opioid receptor agonist and δ-opioid receptor antagonist eluxadoline improved abdominal pain and stool consistency.[39] Kappa-opioid receptor agonists are effective analgesics in visceral pain. Asimadoline, an orally administered kappa opioid-receptor agonist,[40,41] is currently in clinical development for IBS-D.

5-HT Pathways

One proposed pathophysiological pathway in IBS involves neurotransmission through serotonergic nerves that help regulate GI motility, sensation, and secretion. IBS-C is associated with impaired serotonin (5-HT) response.[42] Pharmacotherapies directed at 5-HT receptors therefore offer a promising treatment approach to IBS by stimulating or inhibiting GI motility. The 5-HT4 receptor agonist tegaserod (Zelnorm®, Zelmac®) was indicated for the short-term treatment of women with IBS-C who are <55 years of age, but was refused marketing approval by the European Medicines Agency (EMA) owing to safety concerns.[43] It was previously withdrawn by the US Food and Drug Administration (FDA) in 2007 following postmarketing reports of serious adverse events (AEs), including an increased risk of cardiovascular events, and is currently available only upon request for women who fail to respond to other treatments.[3] Cisapride was also withdrawn as a result of serious cardiac AEs. Other 5-HT4 receptor agonists have failed to demonstrate significant clinical benefit in IBS.[44]

The potential for cardiac and vascular AEs with 5-HT receptor agonists has been demonstrated in other therapeutic areas.[45,46] As a result, any new drugs in this category must demonstrate selectivity for the 5-HT4 receptor over other receptors. Three 5-HT4 receptor agonists in clinical development have greater selectivity for 5-HT4 over other receptors. Prucalopride (Resolor®), a selective, high affinity 5-HT4 receptor agonist, demonstrated efficacy in three large randomised, placebo-controlled, clinical trials of chronic idiopathic constipation (CIC), but has not yet been studied in IBS-C.[47-49] Its most common AE is headache, followed by nausea and diarrhoea. Prucalopride has been approved for use in Europe[50] but not yet in the US. Velusetrag and ATI-7505 are 5-HT4 antagonists in early stage clinical development.[51]

Other therapies targeting the 5-HT system include 5-HT3 antagonists such as cilansetron and alosetron.[52,53] These significantly improve the symptoms of IBS-D but have been associated with ischaemic colitis and constipation. Alosetron was withdrawn from the US market in 2000 and reintroduced in 2002 with availability and use restricted, and the development of cilansetron was stopped.[53] Alosetron is not available in Europe. In a recent study from the UK, ondansetron, a 5-HT3 antagonist approved for the treatment of chemotherapy-induced nausea,

has also been found to be effective for patients with IBS-D.[54] Pumosetrag (DDP-733), an orally available prokinetic agent and locally acting 5-HT3 partial agonist, is currently in clinical development for IBS-C.[55]

Gastrointestinal Secretion

An emerging concept in IBS therapy is the use of non-absorbed, luminally-acting molecules, minimising the likelihood of systemic AEs. Inducing fluid secretion into the GI tract, which softens stools, increases motility, and promotes spontaneous bowel movements, has proved a promising therapeutic target. Currently, two intestinal secretagogues are available: lubiprostone and linaclotide. Clinical trial data demonstrating their efficacy and safety in IBS are summarised in Table 2.

Table 2. Randomised, placebo-controlled trials of linaclotide and lubiprostone in constipation-predominant irritable bowel syndrome (IBS-C).

Author	Study design	Patients (n)	Main outcomes
Linaclotide (100 or 1000 μg)	Phase IIa, n=36, 100% women[96]	5 days	Ascending colon emptying time Time to first bowel movement Stool frequency Stool consistency Ease of stool passage
Linaclotide (75, 150, 300, or 600 μg QD)	Phase IIb, n=420, 92% women[64]	12 weeks	CSBM and SBM frequency CSBM responder SBM responder Adequate relief responder Global relief responder Stool consistency Straining Abdominal pain Abdominal discomfort Bloating
Linaclotide (290 μg QD)	Phase III study, n=804, 90% women[65]	26 weeks	FDA responder CSBM and SBM frequency Abdominal pain, discomfort, bloating, fullness, and cramping Stool consistency Straining Adequate relief Treatment satisfaction
Linaclotide (290 μg QD)	Phase III, n=800, 91% women[66]	12 weeks	FDA responder CSBM and SBM frequency Abdominal pain, discomfort, bloating, fullness, and cramping Stool consistency Straining Adequate relief Treatment satisfaction
Lubiprostone (8 μg BID)	Two Phase III trials, n=1171[58]	12 weeks	Using a balanced seven-point Likert scale ranging from significantly relieved (+3), to significantly worse (-3), patients responded on their electronic diary to the question: 'How would you rate your relief of IBS symptoms over the past week compared to how you felt before you entered the study?'
Lubiprostone (8 μg BID)	Open-label extension study of Phase III trials	36 weeks	Long-term safety and tolerability, monitored via adverse events (AEs), laboratory parameters and vital signs. Monthly responder rates Patient evaluations of IBS-C symptom severity Quality of life

BID: twice daily; QD: once daily; CSBM: complete spontaneous bowel movement; SBM: spontaneous bowel movement.

Table 3: Primary endpoints specified by the European Medicines Agency (EMA) and US Food and Drugs Administration (FDA).

EMA[67]	FDA[68]
Abdominal pain or discomfort responder: 30% reduction in mean abdominal pain or discomfort score, with neither condition worsening from baseline for at least 6 weeks. IBS degree of relief responder: symptoms considerably or completely relieved for at least 6 weeks.	FDA responder: decrease of at least 30% in the average daily worst abdominal pain score (measured daily) compared with baseline weekly average, and an increase of at least one complete spontaneous bowel movement (CSBM) from baseline.

Lubiprostone (Amitiza®) is an analogue of endogenous prostones (bicyclic fatty acids), and directly activates chloride channels in epithelial cell membranes, inducing fluid secretion.[56] It is approved by the FDA for the treatment of CIC and IBS-C. In a Phase II trial, lubiprostone showed significantly greater improvements in mean abdominal discomfort/pain scores after 2 months compared with placebo, but at 3 months the trend was no longer significant.[57] In a combined analysis of two Phase III clinical trials, a significantly higher percentage of lubiprostone-treated patients were considered overall responders compared with those treated with placebo.[58] An extension study found that lubiprostone demonstrated sustained efficacy and was safe and well tolerated over 9–13 months of treatment.[59] Common AEs of lubiprostone include nausea, diarrhoea, abdominal pain, and bloating, and, rarely, dyspnoea.[60] Nausea is mostly mild-to-moderate, and is best managed by taking the drug with food.[35]

Further studies have focused on the mechanism of action of lubiprostone. An 8-week crossover study demonstrated that lubiprostone has no effect on visceral pain thresholds. The reductions in clinical pain associated with its use appear to be secondary to changes in stool consistency.[61] An *in vitro* study found that lubiprostone, but not active linaclotide, promotes repair of the epithelial barrier and cell function, a finding of potential clinical importance for IBS patients with compromised barrier function.[62]

Linaclotide (Constella®) is a first-in-class 14-amino acid peptide agonist of guanylate cyclase (GC-C). It activates GC-C receptors on the luminal surface intestinal enterocytes, causing a signal transduction cascade that results in chloride channel activation and enhanced secretion of intestinal fluid and accelerated intestinal transit.[63] Linaclotide received EMA marketing authorisation in November 2012 and FDA approval in August 2012 for the symptomatic treatment of moderate-to-severe IBS-C in adults after demonstrating efficacy and safety in Phase II[64] and Phase III clinical trials, based on FDA endpoints[65,66] (Table 3),[67,68] as well as an analysis based on EMA recommended endpoints.[69] Linaclotide also significantly improved abdominal symptoms and QoL in a subgroup of patients who rated specific abdominal symptoms as severe at baseline.[70] A higher rate of AEs was reported in the linaclotide treatment arm compared with placebo; however, most were mild or moderate in severity. The most common of these was diarrhoea. The use of linaclotide in clinical practice requires further evaluation of the significance of this AE and the best strategies to minimise its impact. Animal studies have found that linaclotide has an analgesic mechanism of action that is independent of its action on gut motility or stool consistency.[71] Another GC-C agonist, plecanatide, is currently in clinical development for IBS-C, and demonstrated efficacy in a Phase II study of patients with CIC.[72] A Phase II placebo-controlled trial in IBS-C patients is ongoing.[73]

Intestinal Microbiota

Alterations in intestinal microbiota are increasingly being recognised as an important factor in the pathophysiology of IBS. Recent evidence suggests that a proportion of patients with IBS may have small intestinal bacterial overgrowth (SIBO), although this suggestion is controversial.[74-76] This has provided a rationale for antibiotic-based therapies for IBS. Rifaximin

is a nonabsorbable antibiotic that demonstrates no clinically relevant bacterial resistance and has been associated with improvement of IBS symptoms, but symptoms seem to return when the treatment is stopped, and repeated dosing has not been formally evaluated.[77]

Probiotics have also proven safe and effective in IBS, and may be administered as functional foods such as yoghurts and drinks or in pharmaceutical forms. The most widely used probiotics are *Lactobacillus plantarum* 299v, *Lactobacillus rhamnosus LGG*, *Lactobacillus reuteri*, *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium infantis*, *lactis* or *brevis*. However, not all probiotics have been shown to be equally effective. Clinical trials to date have varied in design, probiotic strain used, dosage and formulation, but a number of studies have reported beneficial effects.[78-82] A recent review concluded that probiotics are associated with modest clinical benefits but are unlikely to benefit all patients.[83] A larger body of good quality clinical trial data is needed to draw firm conclusions.

Faecal microbiota transplantation has demonstrated efficacy in recurrent *Clostridium difficile* infections,[84] and interest is growing in the technique as a potential treatment for IBS. However, the technique remains controversial and to date has only been used in experimental settings.[85,86]

OTHER THERAPEUTIC APPROACHES TO IBS

Stress and concomitant psychological conditions such as somatisation, anxiety and depression play a major role in the development, clinical course, and response to treatment in IBS.[87,88] Psychotropic drugs, including selective serotonin/serotonin-norepinephrine receptor antagonists and tricyclic antidepressants, therefore play a key role in the treatment of moderate-to-severe IBS.[89]

It is well known that bile acids in the colon stimulate motility and increase secretion. Following their role in digestion, bile acids are reabsorbed by ileal bile acid transporters (IBATs). Inhibiting IBATs by luminally acting drugs may increase the amount of bile reaching the proximal colon and benefit patients with IBS-C. In a Phase II clinical trial, the IBAT inhibitor A3309 increased stool frequency and improved constipation-related symptoms in CIC.[90] Agents in clinical development for IBS-D include ibodutant, a neurokinin 2 receptor antagonist,[91] anti-inflammatory approaches including mesalazine[92] and ketotifen,[93] and the centrally acting agent dextofisopam.[94]

CONCLUDING REMARKS

Until recently, pharmacotherapy directed at individual symptoms has been the standard of care for IBS. However, new treatments are improving clinical outcomes and changing the treatment algorithm, especially as clinical trial data are becoming available. While systemic prokinetic agents, such as the 5-HT4 receptor agonist prucalopride, and 5-HT3 receptor agonists, offer considerable potential, the largest body of clinical data to date supports the use of the pro-secretory agents - lubiprostone and linaclotide. There is a need for head-to-head trials comparing the efficacy and cost-effectiveness of these treatments.

In conclusion, the treatment armamentarium for IBS is expanding. However, there remains a need for a multidisciplinary and individualised approach to IBS. While some patients will benefit primarily from symptom-based pharmacological treatment, others may benefit more from behavioural therapy and/or the use of psychotropic drugs. A graduated treatment approach has been suggested, with diagnosis being the most important treatment step.[95] Individualising management remains the key to achieving the optimal outcomes in IBS with currently available therapeutics.

REFERENCES

1. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin Gastroenterol Hepatol. 2012;10:712-21. e4.

2. Agarwal N, Spiegel BM. The effect of irritable bowel syndrome on health-related quality of life and health care expenditures. Gastroenterol Clin North Am. 2011;40:11-9.

3. Fortea J, Prior M. Irritable bowel syndrome with constipation: a European-focused systematic literature review of disease burden. J Med Econ. 2013;16:329-41.

4. Hellstrom PM et al. Characteristics of

acute pain attacks in patients with irritable bowel syndrome meeting Rome III criteria, Am J Gastroenterol. 2011;106:1299-307.

5. Longstreth GF et al. Functional bowel disorders. Gastroenterology. 2006;130:1480-91.

6. Spiller R. Clinical update: irritable bowel syndrome. Lancet. 2007;369:1586-8.

7. Patel SM et al. The placebo effect in irritable bowel syndrome trials: a meta-analysis. Neurogastroenterol Motil. 2005;17:332-40.

8. Halland M, Talley NJ. New treatments for IBS. Nat Rev Gastroenterol Hepatol. 2013;10:13-23.

9. Ford AC, Talley NJ. IBS in 2010: advances in pathophysiology, diagnosis and treatment. Nat Rev Gastroenterol Hepatol. 2011;8:76-8.

10. Talley NJ. Green light from the FDA for new drug development in irritable bowel syndrome and functional dyspepsia. Am J Gastroenterol. 2009;104:1339-41.

11. Simren M et al. Food-related gastrointestinal symptoms in the irritable bowel syndrome. Digestion. 2001;63:108-15.

12. Bohn L et al. Self-reported food-related gastrointestinal symptoms in IBS are common and associated with more severe symptoms and reduced quality of life. Am J Gastroenterol. 2013;108:634-41.

13. Halpert A et al. What patients know about irritable bowel syndrome (IBS) and what they would like to know. National Survey on Patient Educational Needs in IBS and development and validation of the Patient Educational Needs Questionnaire (PEQ). Am J Gastroenterol. 2007;102:1972-82.

14. Gibson PR, Shepherd SJ. Evidence-based dietary management of functional gastrointestinal symptoms: The FODMAP approach. J Gastroenterol Hepatol. 2010;25:252-8.

15. Muir JG, Gibson PR. The Low FODMAP diet for treatment of irritable bowel syndrome and other gastrointestinal disorders. Gastroenterol Hepatol (N Y). 2013;9:450-2.

16. Ong DK et al. Manipulation of dietary short chain carbohydrates alters the pattern of gas production and genesis of symptoms in irritable bowel syndrome. J Gastroenterol Hepatol. 2010;25:1366-73.

17. Ford AC et al. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis. BMJ. 2008;337:a2313.

18. Ruepert L et al. Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. Cochrane Database Syst Rev. 2011;CD003460.

19. Bijkerk CJ et al. Soluble or insoluble fibre in irritable bowel syndrome in primary care? Randomised placebo controlled trial. BMJ. 2009;339:b3154.

20. Johannesson E et al. Physical activity improves symptoms in irritable bowel syndrome: a randomized controlled trial. Am J Gastroenterol. 2011;106:915-22.

21. Ford AC et al. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. Gut. 2009;58(3):367-78.

22. Labus J et al. Randomised clinical trial: symptoms of the irritable bowel syndrome are improved by a psycho-education group intervention. Aliment Pharmacol Ther. 2013;37:304-15.

23. Lackner JM et al. How does cognitive behavior therapy for irritable bowel syndrome work? A mediational analysis of a randomized clinical trial. Gastroenterology. 2007;133:433-44.

24. Dobbin A et al. Randomised controlled trial of brief intervention with biofeedback and hypnotherapy in patients with refractory irritable bowel syndrome. J R Coll Physicians Edinb. 2013;43:15-23.

25. Ljotsson B et al. Internet-delivered exposure-based treatment vs. stress management for irritable bowel syndrome: a randomized trial. Am J Gastroenterol. 2011;106:1481-91.

26. Lackner JM et al. The Irritable Bowel Syndrome Outcome Study (IBSOS): rationale and design of a randomized, placebo-controlled trial with 12 month follow up of self- versus clinician-administered CBT for moderate to severe irritable bowel syndrome. Contemp Clin Trials. 2012;33:1293-310.

27. Tonkin-Crine S et al. Exploring patients' views of a cognitive behavioral therapy-based website for the self-management of irritable bowel syndrome symptoms. J Med Internet Res. 2013;15:e190.

28. Roberts L et al. Gut-directed hypnotherapy for irritable bowel syndrome: piloting a primary care-based randomised controlled trial. Br J Gen Pract. 2006;56:115-21.

29. Lindfors P et al. Effects of gut-directed hypnotherapy on IBS in different clinical settings-results from two randomized, controlled trials. Am J Gastroenterol. 2012;107:276-85.

30. Chapman RW et al. Randomized clinical trial: macrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated with irritable bowel syndrome. Am J Gastroenterol. 2013;108:1508-15.

31. Smith MJ et al. Bile acid malabsorption in persistent diarrhoea. J R Coll Physicians Lond. 2000;34:448-51.

32. Walters JR, Pattni SS. Managing bile acid diarrhoea. Therap Adv Gastroenterol. 2010;3:349-57.

33. Gale JD, Houghton LA. Alpha 2 Delta ($\alpha(2)\delta$) Ligands, Gabapentin and Pregabalin: What is the evidence for potential use of these ligands in irritable bowel syndrome. Front Pharmacol. 2011;2:28.

34. Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. Gut. 2011;60:209-18.

35. Saad RJ. Peripherally acting therapies for the treatment of irritable bowel syndrome. Gastroenterol Clin North Am. 2011;40:163-82.

36. Hammerle CW, Surawicz CM. Updates on treatment of irritable bowel syndrome. World J Gastroenterol. 2008;14:2639-49.

37. Camilleri M. Review article: new receptor targets for medical therapy in irritable bowel syndrome. Aliment Pharmacol Ther. 2010;31:35-46.

38. Hanauer SB. The benefits of loperamide in the treatment of patients with IBS or IBD. Introduction. Rev Gastroenterol Disord. 2007;7 Suppl 3:S1-2.

39. Dove LS et al. Eluxadoline benefits patients with irritable bowel syndrome with diarrhea in a phase 2 study. Gastroenterology. 2013;145:329-38. e1.

40. Mangel AW et al. Clinical trial: asimadoline in the treatment of patients with irritable bowel syndrome. Aliment Pharmacol Ther. 2008;28:239-49.

41. Mangel AW, Hicks GA. Asimadoline and its potential for the treatment of diarrhea-predominant irritable bowel syndrome: a review. Clin Exp Gastroenterol. 2012;5:1-10.

42. Spiller R. Recent advances in understanding the role of serotonin in gastrointestinal motility in functional bowel disorders: alterations in 5-HT signalling and metabolism in human disease. Neurogastroenterol Motil. 2007;19 Suppl 2:25-31.

43. EMA, Refusal Assessment Report for Zelnorm. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000621/WC500058849.pdf. Accessed 11 November 2013.

44. Sanger G, Quigley EMM. Constipation, IBs and the 5-HT4 Receptor: what role for prucalopride? Clinical Medicine Insight: Gastroenterology. 2010;3:21-33.

45. Suspension of cisapride (Prepulsid) licences: Product withdrawal; http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con019561.pdf. Accessed 11 November 2011.

46. FDA, FDA Announces Withdrawal Fenfluramine and Dexfenfluramine (Fen-Phen). http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm179871.

htm. Accessed 11 November 2011.

47. Tack J et al. Prucalopride (Resolor) in the treatment of severe chronic constipation in patients dissatisfied with laxatives. Gut. 2009;58:357-65.

48. Quigley EM et al. Clinical trial: the efficacy, impact on quality of life, and safety and tolerability of prucalopride in severe chronic constipation--a 12-week, randomized, double-blind, placebo-controlled study. Aliment Pharmacol Ther. 2009;29:315-28.

49. Camilleri M et al. A placebo-controlled trial of prucalopride for severe chronic constipation. N Engl J Med. 2008;358:2344-54.

50. EMA, European Medicines Angency: Resolor. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001012/human_med_001030.jsp. Accessed 26 November 2013.

51. Tack J et al. Systematic review: cardiovascular safety profile of 5-HT(4) agonists developed for gastrointestinal disorders. Aliment Pharmacol Ther. 2012;35:745-67.

52. Andresen V et al. Effects of 5-hydroxytryptamine (serotonin) type 3 antagonists on symptom relief and constipation in nonconstipated irritable bowel syndrome: a systematic review and meta-analysis of randomized controlled trials. Clin Gastroenterol Hepatol. 2008;6:545-55.

53. Lewis JH. The risk of ischaemic colitis in irritable bowel syndrome patients treated with serotonergic therapies. Drug Saf. 2011;34:545-65.

54. Garsed KH et al. Ondansetron is an effective treatment for patients with diarrhoea predominant irritable bowel syndrome. Gut. 2011;60 (Suppl 3):A40.

55. Evangelista S. Drug evaluation: Pumosetrag for the treatment of irritable bowel syndrome and gastroesophageal reflux disease. Curr Opin Investig Drugs. 2007;8:416-22.

56. Bao HF et al. A synthetic prostone activates apical chloride channels in A6 epithelial cells. Am J Physiol Gastrointest Liver Physiol. 2008;295:G234-51.

57. Johanson JF et al. Clinical trial: phase 2 study of lubiprostone for irritable bowel syndrome with constipation. Aliment Pharmacol Ther. 2008;27:685-96.

58. Drossman DA et al. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome--results of two randomized, placebo-controlled studies. Aliment Pharmacol Ther. 2009;29:329-41.

59. Chey WD et al. Safety and patient outcomes with lubiprostone for up to 52 weeks in patients with irritable bowel syndrome with constipation. Aliment Pharmacol Ther. 2012;35:587-99.

60. Chamberlain SM, Rao SS. Safety evaluation of lubiprostone in the treatment of constipation and irritable bowel syndrome. Expert Opin Drug Saf. 2012;11:841-50.

61. Whitehead WE et al. Lubiprostone does not influence visceral pain thresholds in patients with irritable bowel syndrome. Neurogastroenterol Motil. 2011;23:944-e400.

62. Cuppoletti J et al. Contrasting effects of linaclotide and lubiprostone on restitution of epithelial cell barrier properties and cellular homeostasis after exposure to cell stressors. BMC Pharmacol. 2012;12:3.

63. Busby RW et al. Linaclotide, through activation of guanylate cyclase C, acts locally in the gastrointestinal tract to elicit enhanced intestinal secretion and transit. Eur J Pharmacol. 2010;649:328-35.

64. Johnston JM et al. Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome with constipation. Gastroenterology. 2010;139:1877-86. e2.

65. Chey WD et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. Am J Gastroenterol. 2012;107:1702-12.

66. Rao S et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. Am J Gastroenterol. 2012;107:1714-24; quiz p. 25.

67. EMA, European Medicines Agency. Points to Consider on the Evaluation of Medicinal Products for the Treatment of Irritable Bowel Syndrome. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003187.pdf. Accessed 12 November 2013.

68. FDA, Guidance for Industry. Irritable Bowel Syndrome — Clinical Evaluation of Drugs for Treatment. http://www.fda.gov/downloads/Drugs/Guidances/UCM205269.pdf. Accessed 8 November 2013.

69. Quigley EM et al. Randomised clinical trials: linaclotide phase 3 studies in IBS-C - a prespecified further analysis based on European Medicines Agency-specified endpoints. Aliment Pharmacol Ther. 2013;37:49-61.

70. Rao SS et al. Effect of Linaclotide on Severe Abdominal Symptoms in Patients with Irritable Bowel Syndrome with Constipation. Clin Gastroenterol Hepatol. 2013;doi:10.1016/j.cgh.2013.09.022. [Epub ahead of print].

71. Castro J et al. Linaclotide inhibits colonic nociceptors and relieves abdominal pain via guanylate cyclase-C and extracellular cyclic guanosine 3',5'-monophosphate. Gastroenterology. 2013;145:1334-46.e11.

72. Shailubhai KB et al. Plecanatide, a guanylate cyclase C agonist improves bowel habits and symptoms associated with chronic constipation in a phase IIa clinical study. Am J Gastroenterol. 2011;106:S502.

73. The Plecanatide Irritable Bowel Syndrome With Constipation Study (IBS-C) (CIBS). http://clinicaltrials.gov/show/NCT01722318. Accessed 12 November 2013.

74. Quigley EM, Quera R. Small intestinal bacterial overgrowth: roles of antibiotics, prebiotics, and probiotics. Gastroenterology. 2006;130:S78-90.

75. Simren M et al. Intestinal microbiota in functional bowel disorders: a Rome foundation report. Gut. 2013;62:159-76.

76. Ohman L, Simren M. Intestinal microbiota and its role in irritable bowel syndrome (IBS). Curr Gastroenterol Rep. 2013;15:323.

77. Saadi M, McCallum RW. Rifaximin in irritable bowel syndrome: rationale, evidence and clinical use. Ther Adv Chronic Dis. 2013;4:71-5.

78. Ortiz-Lucas M et al. Effect of probiotic species on irritable bowel syndrome symptoms: A bring up to date meta-analysis. Rev Esp Enferm Dig. 2013;105:19-36.

79. Roberts LM et al. A randomised controlled trial of a probiotic 'functional food' in the management of irritable bowel syndrome. BMC Gastroenterol. 2013;13:45.

80. Ki Cha B et al. The effect of a multispecies probiotic mixture on the symptoms and fecal microbiota in diarrhea-dominant irritable bowel syndrome: a randomized, double-blind, placebo-controlled trial. J Clin Gastroenterol. 2012;46:220-7.

81. Kruis W et al. A double-blind placebo-controlled trial to study therapeutic effects of probiotic Escherichia coli Nissle 1917 in subgroups of patients with irritable bowel syndrome. Int J Colorectal Dis. 2012;27:467-74.

82. Begtrup LM et al. Long-term treatment with probiotics in primary care patients with irritable bowel syndrome--a randomised, double-blind, placebo controlled trial. Scand J Gastroenterol. 2013;48:1127-35.

83. Dai C et al. Probiotics and irritable bowel syndrome. World J Gastroenterol. 2013;19:5973-80.

84. Landy J et al. Review article: faecal transplantation therapy for gastrointestinal disease. Aliment Pharmacol Ther. 2011;34:409-15.

85. van Nood E et al. Fecal microbiota transplantation: facts and controversies. Curr Opin Gastroenterol. 2014;30(1):34-9.

86. Smits LP et al. Therapeutic potential of fecal microbiota transplantation. Gastroenterology. 2013;145:946-53.

87. van Tilburg MA et al. Which psychological factors exacerbate irritable bowel syndrome? Development of a comprehensive model. J Psychosom Res. 2013;74:486-92.

88. Lackner J et al. Patient-reported outcomes for irritable bowel syndrome are associated with patients' severity ratings of gastrointestinal symptoms and psychological factors. Clin Gastroenterol Hepatol. 2011;9:957-64. e1.

89. Dekel R et al. The use of psychotropic drugs in irritable bowel syndrome. Expert Opin Investig Drugs. 2013;22:329-39.

90. Chey WD et al. A randomized placebo-controlled phase IIb trial of a3309, a bile acid transporter inhibitor, for chronic idiopathic constipation. Am J Gastroenterol. 2011;106:1803-12.

91. Tack J et al. Efficacy of Ibodutant, a selective antagonist of Neurokinin 2 receptors, in irritable bowel syndrome with diarrhea (IBS-D): The results of a double-blind, randomized, placebo-controlled, parallel-group phase II study (the IRIS-2). Abstract no 520. Presented at: Digestive Disease Week 2013; May 18-21, Orlando, FL.

92. Leighton MP et al. Efficacy and mode of action of mesalazine in the treatment of diarrhoea-predominant irritable bowel syndrome (IBS-D): study protocol for a randomised controlled trial. Trials. 2013;14:10.

93. O'Sullivan M. Therapeutic potential of ketotifen in irritable bowel syndrome (IBS) may involve changes in mast cells at sites beyond the rectum. Gut. 2011;60:423; author reply.

94. Leventer SM et al. Clinical trial: dextofisopam in the treatment of patients with diarrhoea-predominant or alternating irritable bowel syndrome. Aliment Pharmacol Ther. 2008;27:197-206.

95. Tornblom H, Simrén M. "Sequencing the Treatments: The Book in one Chapter!," Emmanuel A, Quigley EMM (eds.), Irritable Bowel Syndrome: Diagnosis and Clinical Management, First Edition (2013), John Wiley & Sons, Ltd., pp. 227-99.

96. Andresen V et al. Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome. Gastroenterology. 2007;133:761-8.


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UNDERSTANDING THE PATHOPHYSIOLOGY OF IBS

Giovanni Barbara, Marco Dolci, Cesare Cremon, Maria Raffaella Barbaro, Lara Bellacosa, Anita Fucili, Vincenzo Stanghellini

Department of Clinical Medicine and Center for Applied Biomedical Research (CRBA), University of Bologna, Italy

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ABSTRACT

While irritable bowel syndrome (IBS) is still considered a 'disorder of gut function' and is diagnosed on the basis of symptoms, evidence is growing to indicate the existence of biochemical, molecular, immune, and microbiological abnormalities in large subsets of patients. According to the current view, luminal factors (e.g. derived from food, microbiota, and bile acids) permeate into the mucosa through a leaky epithelial barrier. These substances elicit abnormal responses, partly related to the activation of the immune system, which evoke altered neuro-muscular responses and stimulation of pain pathways. This research is providing a new way of thinking about the pathophysiology of IBS and will potentially lead to the development of novel treatments for these common disorders.

Keywords: Irritable bowel syndrome, pathophysiology, intestinal motility, visceral hypersensitivity, post-infectious irritable bowel syndrome, serotonin, microbiota, mucosal permeability, neuro-immune interactions.

INTRODUCTION

The irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder (FGID) affecting between 10-20% of the population. IBS is defined on the basis of symptoms reported by the patients as recurrent abdominal pain or discomfort at least 3 days a month in the previous 3 months, associated with two or more of the following: improvement with defecation, onset associated with a change in frequency of stool, and onset associated with a change in form (appearance) of stool.[1] IBS is further classified according to the predominant bowel habit into diarrhoea predominant IBS (IBS-D), constipation predominant IBS (IBS-C) and mixed bowel pattern IBS (IBS-M).[1] Traditionally IBS has been considered a disorder characterised by a dysfunction in the brain-gut axis, associated with: 1) psychosocial factors; 2) changes in intestinal motility; and 3) increased perception of stimuli arising from the intestine. More recently, several molecular and biochemical abnormalities have been identified. These include genetic polymorphisms, transient gastrointestinal infections, neuro-immune interactions, increased mucosal permeability, altered serotonin metabolism, and the participation of luminal factors, including gut microbiota and dietary factors.[2] These new findings have fuelled the interest in IBS pathophysiology and opened new avenues for the development of specific treatments for this common condition.

PSYCHOSOCIAL FACTORS

In the collective imagination, IBS is a disturbance of young, anxious, otherwise healthy subjects. At the end of the 19th century Sir Wiliam Osler wrote that patients with 'mucous colitis' (what we would consider IBS nowadays) have a normal colonic epithelium and that many of them are hysterical, hypochondriac, self-centred, neurasthenic, and suffered from colicky abdominal pains.[3] Indeed, compared with the general population, IBS patients have a higher prevalence of psychological comorbidity (e.g. affective disorders such as anxiety, hostility and phobia,

history of emotional, physical, and sexual abuse).[4,5] In addition, substantial evidence supports a key role for stress in the pathophysiology of gut motor dysfunction and increased sensitivity in patients with IBS.[6] Nonetheless, it is obvious that psychological factors alone are insufficient to explain the complex, multifaceted manifestations of IBS. Certainly, not all subjects with disturbances of the psychological sphere develop IBS and the prevalence of anxiety, paranoid ideation, hostility, depression, and obsessive-compulsive disorders in patients in community samples is only slightly higher compared with those found in the general population without IBS.[7] In a recent study, a large group of community subjects was followed-up for 12 years in the attempt to detect the relative weight of psychological versus peripheral factors in the pathogenesis of FGID. As expected, the presence of psychological impairment at the beginning of the observational period represented a predictive factor for the development of IBS at the end of follow-up. However, FGID diagnosis at baseline was significantly associated with higher levels of subsequent anxiety and depression at follow-up.[8] Taken together, these data provide support to the notion that long-lasting gut dysfunction may well contribute to the stress, anxiety, and depression experienced by at least a subgroup of patients with IBS.

INTESTINAL MOTILITY

In the past, IBS was termed 'spastic colon' and 'spastic colitis' in support of the concept that IBS is characterised by changes in colonic motor function and mild mucosal irritation. Manometry studies showed altered patterns of colonic and small intestinal motor function, including a higher number of high amplitude contractions (HAPCs),[9] and enhanced responses to meal ingestion,[10] cholecystokinin,[11] or the stress hormone corticotrophin releasing factor.[12,13] Compared with healthy subjects, IBS-D patients show accelerated colonic transit.[14] Conversely, IBS-C patients showed fewer HAPC, reduced motility, and delayed colonic transit.[12] Although in the majority of studies the relationship between motility changes and symptoms was rather poor, one study showed that >90% of HAPC were correlated with the occurrence of abdominal pain.[11] More robust correlations have been described between bowel habit and transit time changes as detected with radiopaque markers or scintigraphy.[14]

VISCERAL HYPERSENSITIVITY

A reduced threshold for perception of visceral stimuli (i.e. visceral hypersensitivity) is a common finding in FGID, including non-cardiac chest pain, functional dyspepsia, and IBS.[15] Visceral hypersensitivity is considered a key element in the pathogenesis of pain perception in patients with IBS.[16] Hypersensitivity to balloon distension of the rectum was initially detected in 95% of IBS patients[17] but subsequently shown to be present only in about half of patients, particularly those with IBS-D.[18] The correlation of visceral hypersensitivity with abdominal pain, quality-of-life, and psychological impairment has been reported to be poor.[14] However, large sample studies showed that, compared with normosensitive IBS patients, those with rectal hypersensitivity had more pain, bloating, and diarrhoea.[19,20] The pathophysiology of visceral hypersensitivity remains incompletely understood, but likely, involving both peripheral and central (i.e. central nervous system) mechanisms.[15] Among peripheral factors, sensitisation of afferent nerve fibres by serotonin or immune activation has been the focus of recent studies (see below, paragraph on serotonin and neuro-immune interactions). Brain imaging studies (e.g. functional magnetic resonance imaging, positron emission tomography) showed that, in response to experimental rectal distension, compared with healthy controls, IBS patients display enhanced activation of areas involved in pain processing (thalamus, insula, anterior circulate cortex).[21] Nonetheless, results of brain activation and reported pain to peripheral stimuli should be considered with caution as they are highly influenced by the patient's emotional status, including anxiety, anticipation of pain, and hypervigilance.[22,23]

INTESTINAL GAS

Bloating is extremely common in patients with FGID and occurs in up to 96% of patients with IBS. Most patients consider this symptom extremely distressing and about two-thirds of them consider it the worst of their symptoms.[24,25] Bloating is more frequent in patients with IBS-C (75%), than in those with IBS-D (41%), and in IBS-C bloating correlated with abdominal distension.[25-27]

There is no evidence that bloating is caused by an increased amount of gas in the intestine.[28] On the other hand Serra et al.[29] showed that 18 out of 20 IBS patients, compared with only 4 of 20 healthy subjects, developed gas retention, gastrointestinal symptoms or abdominal distension (>3 mm girth increment) after an infusion of a gas mixture in the jejunum. These data suggest that impaired handling rather than increased gas plays a role in the development of bloating in patients with IBS.

LUMINAL FACTORS AND MICROBIOTA

Food ingestion often aggravates symptoms in patients with IBS. Attention has been recently directed on fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs), which are poorly absorbed in the small intestine and reach the colon where they are fermented by bacteria with consequent production of gas and stimulation of colonic motor activity. Diets containing low-FODMAPs have been shown to be beneficial in IBS, although the exact role of these diets in IBS and their applicability in everyday practice remains unclear.[30] Non-coeliac gluten sensitivity is another area of great interest as it is potentially involved in symptom development in a subgroup of IBS patients.[31] A randomised, controlled trial of a gluten-containing diet versus a gluten-free diet in IBS-D, showed that those receiving gluten had increased frequency of bowel movements, intestinal permeability, and peripheral blood immune responses.[32]

The introduction of molecular techniques to detect gut microbial communities has renewed interest in intestinal microbiology. The role of microbiota in FGID including IBS has been the subject of an exhaustive recent review.[33] A recent study indicates that although the majority of patients with IBS do not have significant changes in faecal microbiota compared with healthy controls, two clusters of patients showed abnormal Firmicutes: Bacteroidetes-related taxa ratios. Interestingly, these patients showed changes in bowel physiology including altered bowel transit times while those with normal microbiota had more psychological impairment (i.e. anxiety and depression).[34] Altered microbiota can contribute to abnormal bowel physiology and pain perception through the release of numerous metabolites, including the production of short chain fatty acids as a result of fermentation of polysaccharides unabsorbed in the small intestine. Interestingly, IBS patients had increased faecal levels of acetic and propionic acids which correlated with the severity of abdominal pain and bloating.[35] Other effects of abnormal microbiota on bowel physiology could be related to the activation of the innate immune system as shown by increased mucosal expression of toll-like receptor-4 and 5[36] and the luminal release of mucosal beta-defensin-2.[37]

Bile acid malabsorption has been identified in a subgroup of IBS-D patients. Excessive colonic bile acids stimulate secretion and colonic motility and stimulate pain pathways, hence contributing to diarrhoea and abdominal pain. According to a recent study, about 25% of patients with IBS-D had increased levels of intracolonic bile acids as the result of bile acid malabsoption or excessive bile acids biosynthesis in the liver.[38,39] Among the potential mechanisms involved in this effect, of mention are the mutation of bile acids transporter in ileum[40] and the decreased expression fibroblast growth factor 19 (FGF19), which is produced by ileal enterocytes and regulates bile acids synthesis in the hepatocyte through a negative feedback.[41]

MUCOSAL PERMEABILITY

Several structures contribute to the intestinal mucosal barrier, hence regulating intestinal permeability. These include the mucus layer, the enterocytes, and intercellular tight junctions (TJs) positioned between epithelial cells. Disruption of the mucosal barrier leads to mucosal immune activation and stimulation of sensory pain pathways, leading to visceral hypersensitivity and pain perception. Increased mucosal permeability has been first shown in patients with post-infectious IBS (PI-IBS) by means of the lactulose/mannitol method,[42] and subsequently confirmed in patients who developed IBS after a waterborne outbreak of gastroenteritis in Walkerton, Ontario.[43] Increased intestinal permeability has been documented also in patients with non-specific IBS.[44] Electron microscopy studies showed enlarged paracellular spaces and cytoskeleton condensation suggestive of TJ dysfunction in the jejunum of IBS-D patients.[45] Piche et al.[46] demonstrated that colonic biopsies had significantly higher permeability

compared with controls. Increased permeability was associated with significantly lower expression of tissue zonula occludens mRNA (one of the main TJ components) compared to asymptomatic controls. In addition, mucosal supernatants of patients with IBS, but not from healthy controls, markedly increased permeability of epithelial cell monolayers.[46] Although the origin of these mediators remains unknown, proteases, which are produced in excess by intestinal mast cells or by luminal bacteria, are likely participant in increased mucosal permeability. The trigger factors involved in the increased intestinal permeability of IBS remain elusive. Recent studies suggest the participation of stress,[47] food allergy[48] or gluten.[32]

GASTROINTESTINAL INFECTIONS

Up to now, acute infectious gastroenteritis is the strongest known risk factor for the development of IBS, with a relative risk around 12.[49] PI-IBS may develop after bacterial infection (e.g. *Shigella*, *Salmonella,* and *Campylobacter*) or viral gastroenteritis.[50] Risk factors for PI-IBS comprise the virulence of the pathogen, younger age, female sex, the long duration of the initial gastroenteritis, the use of antibiotics, and psychological factors.[50] Genetic factors, including polymorphisms for genes involved in the control of pro-inflammatory cytokine production (IL-6), host-bacteria interactions and epithelial paracellular permeability, have been demonstrated in patients with PI-IBS.[51] More than half of these patients also have a mild immune activation including higher numbers of mast cells, intraepithelial lymphocytes, lamina propria T cells, calprotectin-positive macrophages, and enteroendocrine cells likely contributing to pain and abdominal pain perception (see below).[50]

NEURO-IMMUNE INTERACTIONS

The development of IBS after infectious gastroenteritis and the higher prevalence of IBS-like symptoms in patients with inflammatory bowel diseases in remission, microscopic colitis or coeliac disease on a gluten free diet, support the potential involvement of immune activation in the pathogenesis of IBS.[52] While there is no evidence of elements typical of acute inflammation or mucosal architecture distortion, a high proportion of these patients has higher mucosal counts of mast cells, T cells and B cells along with increased release of immune mediators (e.g. cytokines, prostanoids, histamine, and proteases).[52] In our laboratory we have introduced the use of mucosal biopsy supernatants in the assessment of the impact of the mucosal milieu on bowel physiology. This is obtained by applying colonic supernatants obtained from IBS patients or controls to intestinal tissues of laboratory animals or human colon specimens obtained from the disease-free margins of surgical resections for colon carcinoma.

Our studies showed that IBS supernatants, infused through a mesenteric artery of the isolated intestinal rat loop, elicited higher sensory fibre activation compared to control supernatants.[53] These effects were significantly inhibited by antagonists of the histamine receptor type-1, proteases inhibitors and serotonin type-3 receptor antagonists, suggesting the participation of mast cells and enterochromaffin cells releasing serotonin in the sensory activation in IBS.[53] Cenac et al.[54] showed that intracolonic injection of IBS supernatants in mice evoked visceral hypersensitivity. This effect was blunted in proteinase activated-2 receptor knock-out mice implying the participation of proteases acting on PAR-2 receptors on sensory nerves.[54] Using sophisticated computerised optical techniques, Buhner et al.[55] showed a rapid histamine, serotonin, and protease-dependent hyper-activation of human enteric nerves in response to IBS supernatants. Although most of these effects could be reduced by inhibitors/antagonists of immune mediators or serotonin, a potential implication of factors derived from luminal bacteria has also been proposed.[56] In addition, the severity and frequency of perceived abdominal painful sensations in IBS patients were directly correlated with the number of activated mast cells in proximity of nerve endings.[57] Thus, taken together, these studies provide not only evidence of infiltration of immune cells in subgroups of patients with IBS, but also implications of immune activation for disturbed intestinal function.

SEROTONIN

Serotonin, or 5-hydroxytryptamine (5-HT), is released by enterochromaffin cells in response to mechanical and chemical stimuli (food, short chain fatty acids produced by intestinal microbiota). 5-HT regulates and generally stimulates secretory, motor, and sensory functions

of the gastrointestinal tract acting on receptors spread all over the gut. 5-HT biological activity is terminated by the serotonin reuptake transporter (SERT) located on enterocytes.[58] The potential role of 5-HT in IBS is supported by the therapeutic efficacy of 5-HT 3 receptor antagonists and 5-HT 4 receptor agonists on IBS symptoms.[59] Decreased postprandial 5-HT platelet-depleted plasma levels have been detected in patients with IBS-C, suggesting a problem with 5-HT release to physiological stimuli.[60] Increased plasma levels of 5-HT have been shown under fasting and fed conditions in patients with IBS-D or PI-IBS, suggesting a reduced 5-HT reuptake and/or metabolism.[61] Although several studies demonstrated a reduced SERT expression in the colon of patients with IBS,[62] conflicting data have been reported. We showed that the spontaneous release of 5-HT was significantly increased in patients with IBS irrespective of bowel habit and correlated with the severity of abdominal pain.[63]

GENETIC FACTORS

Overall, IBS exhibits typical features of a complex disorder with interactions between environmental and genetic factors. Epidemiological studies of familial aggregation and twins suggest a role of genetic predisposition in the incidence of IBS, although social learning is probably at least as important.[64] Several studies assessed the risk effects of single nucleotide polymorphisms (SNPs) in IBS candidate genes. However, at present, our knowledge on genetic predisposition to IBS remains limited. Previous small studies identified polymorphisms in serotonergic[65] and inflammatory genes as susceptibility SNPs for IBS.[66] As previously mentioned in this review, SNPs in genes involved in immune activation, epithelial barrier and host-microbiota interaction (TLR9, IL-6, and CDH1) were associated with PI-IBS.[51] Another study correlated colonic transit and pain sensation with polymorphisms in the neuropeptide S receptor gene (NPSR1), a gene involved in inflammation, anxiety and nociception.[67] A functional Klothoβ gene variant regulating hepatic bile acid synthesis was associated with colonic transit in IBS-D.[68] In the largest genetic study of IBS, Zucchelli et al.[69] demonstrated in two independent cohorts from Sweden and USA a strong association between rs4263839 in TNFSF15 and IBS, particularly IBS-C. The association between this gene which is involved in Th17 immune response and IBS (although in this case with a different subtype, i.e. IBS-D) was recently replicated in UK individuals. In this study, polymorphisms in TNF were also associated with PI-IBS.[70]

CONCLUSIONS

Biochemical, genetic, metabolic, microbiological, molecular, and genetic factors can be now identified in large subgroups of patients with FGID in general and IBS in particular. These findings will likely influence the way we consider and classify these disorders and provide the basis for the development of novel pharmacological and non-pharmacological approaches. These have been recently reviewed elsewhere and include, new 5-HT4 agonists, and 5-HT3 antagonists, 5-HT synthesis inhibitors, m-opioid antagonists, chloride channel openers, guanylate cyclase-c agonists, inhibitor of ileal bile acid transporter, spherical carbon adsorbers, new probiotics and non-absorbable antibiotics, mast cell stabilisers, and 5-aminosalicylates.[71]

REFERENCES

1. Longstreth GF et al. Functional bowel disorders. Gastroenterology. 2006;130:1480-91.

2. Barbara G, Stanghellini V. Biomarkers in IBS: when will they replace symptoms for diagnosis and management? Gut. 2009;58:1571-5.

3. Osler W. The principles and practice of medicine: designed for the use of practitioners and students of medicine (1892), New York: D Appleton and company.

4. Corney RH, Stanton R. Physical symptom severity, psychological and social dysfunction in a series of outpatients with irritable bowel syndrome. J Psychosom Res. 1990;34:483-91.

5. Talley NJ et al. Gastrointestinal tract symptoms and self-reported abuse: a population-based study. Gastroenterology. 1994;107:1040-9.

6. Mayer EA, Tillisch K. The brain-gut axis in abdominal pain syndromes. Annu Rev Med. 2011;62:381–96.

7. Locke GR 3RD et al. Psychosocial factors are linked to functional gastrointestinal disorders: a population based nested case-control study. Am J Gastroenterol. 2004;99:350-7.

8. Koloski NA et al. The brain-gut pathway in functional gastrointestinal disorders is bidirectional: a 12-year prospective population-based study. Gut. 2012;61:1284-90.

9. Kellow JE, Phillips SF. Altered small bowel motility in irritable bowel syndrome is correlated with symptoms. Gastroenterology. 1987;92:1885-93.

10. McKee DP, Quigley EM. Intestinal

motility in irritable bowel syndrome: is IBS a motility disorder? Part 1. Definition of IBS and colonic motility. Dig Dis Sci. 1993;38:1761-72.

11. Chey WY et al. Colonic motility abnormality in patients with irritable bowel syndrome exhibiting abdominal pain and diarrhea. Am J Gastroenterol. 2001;96:1449-506.

12. Whitehead WE et al. Irritable bowel syndrome: physiological and psychological differences between diarrhea-predominant and constipation-predominant patients. Dig Dis Sci. 1980;25:403-13.

13. Fukudo S et al. Impact of corticotrophin-releasing hormone on gastrointestinal motility and adrenocorticotrophin hormone in normal controls and patients with irritable bowel syndrome. Gut. 1998;42:845-9.

14. Camilleri M et al. Prospective study of motor, sensory, psychologic, and autonomic functions in patients with irritable bowel syndrome. Clin Gastroenterol Hepatol. 2008;6:772-81.

15. Barbara G et al. Mechanisms underlying visceral hypersensitivity in irritable bowel syndrome. Curr Gastroenterol Rep. 2011;13:308-15.

16. Whitehead WE et al. Tolerance for rectosigmoid distension in irritable bowel syndrome. Gastroenterology. 1990;98(5 Pt 1):1187-92.

17. Mertz H et al. Altered rectal perception is a biological marker of patients with irritable bowel syndrome. Gastroenterology. 1990;109:40-52.

18. Prior A et al. Anorectal manometry in irritable bowel syndrome: differences between diarrhoea and constipation predominant subjects. Gut. 1990;31:458-62.

19. Posserud I et al. Altered rectal perception in irritable bowel syndrome is associated with symptom severity. Gastroenterology. 2007;133:1113–23.

20. van der Veek PP et al. Symptom severity but not psychopathology predicts visceral hypersensitivity in irritable bowel syndrome. Clin Gastroenterol Hepatol. 2008;6:321–8.

21. Mertz H et al. Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distension. Gastroenterology. 2000;118:842-8.

22. Accarino AM et al. Attention and distraction: effects on gut perception. Gastroenterology. 1997;113:415–22.

23. Elsenbruch S et al. Patients with irritable bowel syndrome have altered emotional modulation of neural responses to visceral stimuli. Gastroenterology. 2010;139:1310–9.

24. Houghton LA, Whorwell PI. Towards a better understanding of abdominal bloating and distension in functional gastrointestinal disorders. Neurogastroenterol Motil. 2005;17:500-11.

25. Houghton LA et al. Relationship of abdominal bloating to distension in irritable bowel syndrome and effect of bowel habit. Gastroenterology. 2006;131:1003-10.

26. Tremolaterra F et al. Intestinal tone and gas motion. Neurogastroenterol Motil. 2006;18:905-10.

27. Accarino AM et al. Abdominal distension results from caudo-ventral redistribution of contents. Gastroenterology. 2009;136:1544-51.

28. Gasbarrini A et al. 1st Rome H2-Breath Testing Consensus Conference Working Group. Methodology and indications of H2-breath testing in gastrointestinal diseases: the Rome Consensus Conference. Aliment Pharmacol Ther. 2009;29 Suppl 1:1-49.

29. Serra J et al. Impaired transit and tolerance of intestinal gas in the irritable bowel syndrome. Gut. 2001;48:14-9.

30. Shepherd SJ et al. Dietary triggers of abdominal symptoms in patients with irritable bowel syndrome: randomized placebo-controlled evidence. Clin Gastroenterol Hepatol. 2008;6:765-71.

31. Biesiekierski JR et al. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. Am J Gastroenterol. 2011;106:508-14.

32. Vazquez-Roque MI et al. A controlled trial of gluten-free diet in patients with irritable bowel syndrome-diarrhea: effects on bowel frequency and intestinal function. Gastroenterology. 2013;144:903-11.

33. Simrén M et al. Rome Foundation Committee. Intestinal microbiota in functional bowel disorders: a Rome foundation report. Gut. 2013;62:159-76.

34. Jeffery IB et al. An irritable bowel syndrome subtypes defined by species-specific alterations in faecal microbiota. Gut. 2012;61:997-1006.

35. Tana C et al. Altered profiles of intestinal microbiota and organic acids may be the origin of symptoms in irritable bowel syndrome. Neurogastroenterol Motil. 2010;22:512-9.

36. Brint EK et al. Differential expression of toll-like receptors in patients with irritable bowel syndrome. Am J Gastroenterol. 2011;106:329-36.

37. Langhorst J et al. Elevated human beta-defensin-2 levels indicate an activation of the innate immune system in patients with irritable bowel syndrome. Am J Gastroenterol. 2009;104:404–10.

38. Camilleri M et al. Measurement of serum 7alpha-hydroxy-4-cholesten-3-one (or7alphaC4), a surrogate test for bile acid malabsorption in health, ileal disease and irritable bowel syndrome using liquid chromatography-tandem mass spectrometry. Neurogastroenterol Motil. 2009;21:e734-43.

39. Wong BS et al. Increased bile acid biosynthesis is associated with irritable bowel syndrome with diarrhea. Clin Gastroenterol Hepatol. 2012;10:1009-15.

40. Montagnani M et al. Absence of dysfunctional ileal sodium-bile acid cotransporter gene mutations in patients with adult-onset idiopathic bile acid malabsorption. Scand J Gastroenterol. 2001;36:1077-80.

41. Walters JR et al. A new mechanism for bile acid diarrhea: defective feedback inhibition of bile acid biosynthesis. Clin Gastroenterol Hepathol. 2009;7:1189-94.

42. Spiller RC et al. Increased rectal mucosa enteroendocrine cells t lymphocytes, and increased gut permeability following acute Campylobacter enteritis and in post-dysenteric irritable bowel syndrome. Gut. 2000;47:804-11.

43. Marshall JK et al. WEL Investigators. Intestinal permeability in patients with irritable bowel syndrome after a waterborne outbreak of acute gastroenteritis in Walkerton, Ontario. Aliment Pharmacol Ther. 2004;20:1317-22.

44. Rao AS et al. Urine sugars for in vivo gut permeability: validation and comparisons in irritable bowel syndrome-diarrhea and controls. Am J Physiol Gastrointest Liver Physiol. 2011;301:G919-28.

45. Martínez C et al. Diarrhoea-predominant irritable bowel syndrome: an organic disorder with structural abnormalities in the jejunal epithelial barrier. Gut. 2013;62:1160-8.

46. Piche T et al. Impaired intestinal barrier integrity in the colon of patients with irritable bowel syndrome: involvement of soluble mediators. Gut. 2009;58:196-201.

47. Vanuytsel T et al. Psychological stress and corticotrophin-releasing hormone increase intestinal permeability in humans by a mast-cell dependent mechanism. Gut. 2013;doi:10.1136/gutjnl-2013-305690.

48. Vivinus-Nébot M et al. Combination of allergic factor scan worsen diarrheic irritable bowel syndrome: role of barrier defects and mast cells. Am J Gastroenterol. 2012;107:75-81.

49. Rodriguez LA, Ruigomez A. Increased risk of irritable bowel syndrome after bacterial gastroenteritis: cohort study. BMJ. 1999;318:565-6.

50. Spiller R, Garsed K. Postinfectious irritable bowel syndrome. Gastroenterology. 2009;136:1979-88.

51. Villani AC et al. Genetic risk factors for post-infectious irritable bowel syndrome following a waterborne outbreak of

gastroenteritis. Gastroenterology. 2010;138:1502-13.

52. Barbara G et al. The immune system in irritable bowel syndrome. J Neurogastroenterol Motil. 2011;17:349-59.

53. Barbara G et al. Mast cell-dependent excitation of visceral-nociceptive sensory neurons in irritable bowel syndrome. Gastroenterology. 2007;132:26-37.

54. Cenac N et al. Role for protease activity in visceral pain in irritable bowel syndrome. J Clin Invest. 2007;117:636-47.

55. Buhner S et al. Activation of human enteric neurons by supernatants of colonic biopsy specimens from patients with irritable bowel syndrome. Gastroenterology. 2009;137:1425-34.

56. Steck N et al. Bacterial proteases in IBD and IBS. Gut. 2012;61:1610-8.

57. Barbara G et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. Gastroenterology. 2004;126:693-702.

58. Gershon MD. 5-Hydroxytryptamine (serotonin) in the gastrointestinal tract. Curr Opin Endocrinol Diabetes Obes. 2013;20:14-21.

59. Camilleri M. Pharmacology of the new treatments for lower gastrointestinal motility disorders and irritable bowel syndrome. Clin Pharmacol Ther. 2012;91:44-59.

60. Shekhar C et al. Rome III functional constipation and irritable bowel syndrome with constipation are similar disorders within a spectrum of sensitization, regulated by serotonin. Gastroenterology. 2013;145:749-57.

61. Atkinson W et al. Altered 5-hydroxytryptamine signaling in patients with constipation- and diarrhea-predominant irritable bowel syndrome. Gastroenterology. 2006;130:34–43.

62. Coates MD et al. Molecular defects in mucosal serotonin content and decreased serotonin reuptake transporter in ulcerative colitis and irritable bowel syndrome. Gastroenterology. 2004;126:1657-64.

63. Cremon C et al. Intestinal serotonin release, sensory neuron activation, and abdominal pain in irritable bowel syndrome. Am J Gastroenterol. 2011;106:1290-8.

64. Levy RL et al. Irritable bowel syndrome in twins: heredity and social learning both contribute to etiology. Gastroenterology. 2001;121:799-804.

65. Camilleri M et al. Serotonin-transporter polymorphism pharmacogenetics in diarrhea predominant irritable bowel syndrome. Gastroenterology. 2002;123:425-32.

66. Gonsalkorale WM et al. Interleukin 10 genotypes in irritable bowel syndrome: evidence for an inflammatory component? Gut. 2003;52:91-3.

67. Camilleri M et al. Neuropeptide S receptor induces neuropeptide expression and associates with intermediate phenotypes of functional gastrointestinal disorders. Gastroenterology. 2010;138:98–107.

68. Wong BS et al. Klothoβ variant mediates protein stability and associates with colon transit in irritable bowel syndrome with diarrhea. Gastroenterology. 2011;140:1934-42.

69. Zucchelli M et al. Association of TNFSF15 polymorphism with irritable bowel syndrome. Gut. 2011;60:1671–7.

70. Swan C et al. Identifying and testing candidate genetic polymorphisms in the irritable bowel syndrome (IBS): association with TNFSF15 and TNFα. Gut. 2012;62:985–94.

71. Camilleri M. Pharmacological agents currently in clinical trials for disorders in neurogastroenterology. J Clin Invest. 2013;123:4111-20.

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PRACTICAL EVALUATION AND HANDLING OF PATIENTS WITH IRRITABLE BOWEL SYNDROME

Bodil Ohlsson

Department of Clinical Sciences, Division of Internal Medicine, Skåne University Hospital, Malmö, Lund University, Lund, Sweden

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ABSTRACT

Irritable bowel syndrome (IBS) is a functional bowel disorder by unknown aetiology. Several reviews are written about pharmacological and psychological treatment of the disease. Nevertheless, healthcare professionals consider these patients difficult to handle in daily practice. There is an uncertainty about how to measure symptoms and to evaluate the effect of any given treatment. In the absence of objective markers, professionals feel unsure of how to manage the condition and the patients do not feel that they are taken seriously. The development of the short, self-reported questionnaire, Visual Analogue Scale for Irritable Bowel Syndrome (VAS-IBS), offers a practical guide to objective measurement of symptoms and effect of given treatments into numerical values in the daily practice.

Keywords: Irritable bowel syndrome, Visual Analogue Scale for Irritable Bowel Syndrome (VAS-IBS), practical handling, treatment evaluation.

BACKGROUND

Abdominal pain and discomfort in combination with altered bowel habits are very common in the population. Mostly, the complaints are not accomplished by organic changes, detectable at clinical routine examinations. When no organic explanation is at hand, the complaints are called functional gastrointestinal disorders (FGID).[1] The most common among these functional disorders are functional dyspepsia and irritable bowel syndrome (IBS). There is comorbidity between various functional disorders, and between functional disorders and affective disturbances.[2] The aetiology to FGID is uncertain, but inflammatory and endocrine factors have been discussed in the pathophysiology.[3-5] Lifestyle factors such as ingestion of some foods, smoking, and lack of physical activity, may be of importance for disease development and maintenance of symptoms.[6-9]

IBS is the most well-defined of the functional disorders. This syndrome has a prevalence of 10-15% in the general population, and it constitutes the most common diagnosis in primary care with half of the patients referred to a specialist in gastroenterology.[10] Although no changes are apparent in clinical examinations, findings which differ from healthy controls have been described in the brain, the enteric nervous system (ENS), and the intestinal wall when examined by experimental procedures.[3-5,11,12] The diagnosis of IBS is based on the presence of abdominal pain and discomfort in combination with symptoms of altered bowel habits for at least 3 of the last 6 months, without any other explanation such as inflammation, tumour or allergy.[1] Due to the high frequency of the disease and the chronic character of the symptoms, IBS constitutes a great problem, both for the individual patient and for the society, with a high degree of absenteeism from work, difficulties to handle daily life, and a reduced health-related quality of life (HRQOL).[10,13-15] Furthermore, IBS is associated with a higher degree of anxiety in close relations, bad self-esteem, and impaired coping mechanisms.[16]

Due to the absence of organic hall-markers, IBS is considered a difficult disorder for the physician to objectively assess concerning the degree of symptoms and responsiveness to drug treatment.

When patients are presenting themselves at a consultation, it is often difficult to identify the most troublesome symptom, and thus, the first choice of treatment. It is important for the physician to detect differences in the main areas of complaints related to bowel symptoms: abdominal pain, diarrhoea, constipation, bloating/flatulence, vomiting/nausea, and abnormal bowel passage. There is a need to translate the patients´ perception of their symptoms and subjective wellbeing into numbers, which can be used and compared over time, in the same way as in organic bowel diseases. Several questionnaires are available to assess symptoms and HRQOL for research use,[17,18] but few tools are available for clinical handling of the patients.

THE VISUAL ANALOGUE SCALE FOR IRRITABLE BOWEL SYNDROME

The Visual Analogue Scale for Irritable Bowel Syndrome (VAS-IBS) was designed as a short, patient-reported questionnaire to be used in clinical practice as a complement to the case history and to detect differences in the patients´ symptoms. Besides physical health problems, IBS also has a negative influence on a person´s psychological wellbeing as well as on daily life.[19] Questions related to these psychological aspects were therefore included in the questionnaire. The VAS was chosen since it had earlier been used to measure symptoms in patients with IBS.[20] The VAS is preferable to graded scales since the steps between the descriptive terms are not known, the respondents´ view of the meaning of a word may not correspond to the researchers´ view, and there is a risk for clustering of responses beside the labels.[21] Furthermore, the VAS can be used independent of language and cultural difficulties.[22] The patients are asked to record in the VAS-IBS, the overall severity of each of the items on a 100 mm-long horizontal line, where 0 corresponds to very severe symptoms and 100 corresponds to no symptoms at all.[22] The response choice "yes" or "no" were chosen for the two questions concerning urgency and feeling of incomplete evacuation of the bowel passage, because it is more important to know whether these symptoms are present or not, rather than the grade of discomfort.

The final VAS-IBS includes seven items answered on a VAS, namely, abdominal pain, diarrhoea, constipation, bloating/flatulence, vomiting/nausea, perception of psychological wellbeing, and the influence of gastrointestinal symptoms on daily life, and the two questions concerning urgency and feeling of incomplete evacuation of the bowel passage, answered by yes or no (Figure 1).

The VAS-IBS has been psychometrically tested for content and criterion validity, scale, acceptability, item-reduction, internal reliability consistency, simplicity, and speed.[23] The Gastrointestinal Symptom Rating Scale (GSRS) and the Psychological General Well-Being Index (PGWB) were chosen as comparable questionnaires to test the criterion validity of the VAS-IBS.[17,18] The psychometric testing confirmed that the VAS-IBS is an acceptable, homogeneous, patient-reported questionnaire with content and criterion validity and internal consistency reliability, which captures the main physical symptoms in the IBS patient, as well as the disease influence on psychological wellbeing and daily life. The VAS was confirmed relevant for the questionnaire with a floor and ceiling effect beneath 20%.[23] It takes only a few minutes for the patients to complete the questionnaire and no manual is needed. Just by looking at the marks on the line, made by the patient, the healthcare professional can get an opinion of the patients´ main symptom, and thus, the treatment strategy can be planned. In addition, the VAS items can be measured by a ruler, and used for research as a continuous variable.

Patients suffering from IBS may have difficulties in assessing whether the clinical symptoms have improved after treatment or not; especially since the disease course is fluctuating over time, and spontaneous improvements are found. After the initial psychometric testing,[23] there was a need for clinical testing as well. In the clinical setting, correlations between how the women experienced improvement and impairment in physical symptoms, psychological wellbeing, and influence on daily life, and the change in the VAS-IBS were found.[24] The reliability was confirmed by test-retest, without any significant difference between the first and second occasions of completion.[24] Thus, the instrument can be used to evaluate the effect of treatment in an objective, numeric manner and to follow the patient over time.

Apart from being compared to GSRS and PGWB,[23,24] further comparison with Experiences in Close Relationships (ECR-36), Rosenberg Self-Esteem Scale (RSES), and Sense of Coherence

Patient ID _____ Date _____

Answers on the first visit to the health provider:

For how long have you had stomach and/or bowel problems? _____

How have you been feeling during the past two weeks concerning abdominal pain?

Very bad _____ Very good

How have you been feeling during the past two weeks concerning diarrhoea?

Very bad _____ Very good

How have you been feeling during the past two weeks in view of constipation?

Very bad _____ Very good

How have you been feeling during the past two weeks concerning bloating and flatulence?

Very bad _____ Very good

How have you been feeling during the past two weeks concerning vomiting and nausea?

Very bad _____ Very good

How have you been feeling during the past two weeks concerning your psychological wellbeing?

Very bad _____ Very good

How much/little have your gastrointestinal problems influenced your daily life over the past two weeks?

Very much _____ Not at all

Have you during the past two weeks felt an urgency to defecate?

YES ☐ NO ☐

Have you during the past two weeks felt that your bowel has not been completely empty after visiting the toilet?

YES ☐ NO ☐

Figure 1. The final English version of the Visual Analogue Scale for Irritable Bowel Syndrome.

(SOC-13) have been performed.[25] The aim of the study was to evaluate the correlation between the patient´s perception of psychological wellbeing and intestinal symptoms´ influence on daily life, and also between anxiety and avoidance in close relationships, the degree of self-esteem, and coping mechanisms, respectively. A perception of poor psychological wellbeing correlated to a high degree of anxiety, low self-esteem, and impaired coping mechanisms. The overall VAS-IBS showed a high degree of internal consistency reliability, as indicated by a Cronbach's alpha coefficient of 0.793, where each of the items had a high alpha value (0.721–0.806) if the item was deleted.[25] Thus, the single item about overall psychological wellbeing demonstrated a psychological state in accordance with other more time-consuming questionnaires, not suitable for clinical use.[26-28]

PATIENT GROUPS

As each gastrointestinal symptom is assessed separately, the instrument can be used independently of an IBS subgroup, and independently of various aetiologies to the

symptom development.[24,25,29] This may be of importance as the IBS population probably is heterogeneous with several different aetiologies, both within and between subgroups.[30]

Functional bowel symptoms may be present secondary to other organic diseases, e.g. Sjögren´s syndrome and inflammatory bowel disease (IBD).[31,32] Sometimes, it is very difficult to clinically differ between motility disorders such as enteric dysmotility and IBS, without making advanced examinations.[33] In order to examine the ability for the instrument to discriminate between different bowel diseases, patients with gastrointestinal dysmotility, IBS, and functional bowel symptoms secondary to Sjögren's syndrome, had to complete the VAS-IBS.[29] Healthy controls had almost no gastrointestinal complaints at all. Patients with gastrointestinal complaints secondary to Sjögren's syndrome had less severe symptoms than patients with primary bowel diseases, but the VAS-IBS did not differ between IBS and gastrointestinal motility disorders.[29]

Patients with IBD and microscopic colitis may have concomitant IBS-like symptoms apart from their inflammatory disease.[32,34] The study performed in microscopic colitis showed that VAS-IBS may be beneficial also in inflammatory bowel diseases to assess IBS-like symptoms.[34]

DISCUSSION

Since functional gastrointestinal complaints are common and lead to impairments in the daily life of the patient and her/his family, there is a need for an appropriate care of these patients. Mostly, patients with organic disorders, such as tumours and inflammation, have a higher priority in clinical practice, and patients with functional disorders are disadvantaged. Although IBS and other functional disorders may not lead to death or other severe complications, the reduced HRQOL and inability to handle daily life have a great impact on the individual patient.[10,13,15] Our study showed that patients with IBS assessed their own symptoms as severe as the patients with dysmotility; although the latter were on parenteral nutrition and used strong analgesics, and were defined by the physicians as much sicker.[29] The economic burden of IBS for the society may be considerable.[14] As the patients often have comorbidity with affective disturbances[2] and the lack of objective signs to follow and evaluate treatment, the patients with IBS are considered to be difficult to handle in the clinical practice. Healthcare professionals who work in somatic care may feel unsure of how to manage conditions where identifiable, pathophysiological markers do not occur.

The relationship between the patient and the healthcare professional is central to how patients perceive their illness.[35] The inability of healthcare professionals to understand the experiences of patients with IBS can act as a barrier in the treatment and interaction between professionals and their patients. There are several reports, which describe that patients with IBS feel that they have been treated with ignorance and lack of respect at the consultation with the healthcare givers.[36] Thus, there is a great need for a better handling in the clinical practice of these patients and a need of education, both for the patients and for the healthcare professionals.[37] Patients need to feel that her/his symptoms are taken seriously and the VAS-IBS can preferably be used to confirm the patients' physical symptoms and psychological wellbeing. Healthcare professionals need to acknowledge and affirm the patients' perspective of IBS, and the main thing is to build up a trust between the patient and the healthcare giver.[36]

To be able to assess the patients' symptoms by numerical values gives an objective marker of the symptoms to both healthcare professionals and patients. This can make the healthcare givers feel more secure when in contact with the patients, and the patients perceive that there is a measurement performed and the symptoms are confirmed. By objectively measuring the symptoms, one can postulate whether a drug improves the symptoms and can be exposed, this is not always properly evaluated. The previously developed IBS-Severity Scoring System (IBS-SSS) is similar to VAS-IBS in the simplicity, but it does not include the item intestinal symptoms´ influence on daily life; altered bowel habits are also included in the same item, independent of diarrhoea and constipation.[38]

Patients with IBS require a unique set of self-care activities, including adherence to medication regimens,[9] lifestyle and dietary changes,[29] physical activity,[40] stress management, and psychological treatment[41] to be able to live with this condition. A good practical handling and relationship between professionals and patients are rudimentary to

facilitate this treatment, which demands a great effort by the patient to change his/her lifestyle habits and mind.

CONCLUSIONS

The VAS-IBS is a brief, patient-reported questionnaire suitable for use in daily consultations. It offers a practical guide for the healthcare professionals to affirm the patients´ complaints and to give numeric values of the symptoms. The VAS-IBS can also be used to evaluate the effect of prescribed drugs and changes in lifestyle factors since it can be used over time. This questionnaire can be a useful complement to the medical care of patients with IBS.

REFERENCES

1. Drossman DA. The functional gastrointestinal disorders and the Rome III process. Gastroenterology. 2006;130:1377-90.

2. Surdea-Blaga T, Băban A, Dumitrascu DL. Psychosocial determinants of irritable bowel syndrome. World J Gastroenterol. 2012;21:616-26.

3. Spiller RC et al. Increased rectal mucosal enteroendocrine cells, T lymphocytes, and increased gut permeability following acute Campylobacter enteritis and in post-dysenteric irritable bowel syndrome. Gut. 2000;47:804-11.

4. Dunlop SP et al. Distinctive clinical, psychological, and histological features of postinfective irritable bowel syndrome. Am J Gastroenterol. 2003;93:1578-83.

5. Barbara G et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. Gastroenterology. 2004;126:693-702.

6. Parry SD et al. Factors associated with the development of post-infectious functional gastrointestinal diseases: does smoking play a role? Eur J Gastroenterol Hepatol. 2005;17:1071-5.

7. Pisinger C et al. The association between active and passive smoking and frequent pain in a general population. Eur J Pain. 2011;15:77-83.

8. Kang SH et al. The effects of lifestyle modification on symptoms and quality of life in patients with irritable bowel syndrome: a prospective observational study. Gut Liver. 2011;5:472-7.

9. Spiller RC. Irritable bowel syndrome: gender, infection, lifestyle or what else?

Dig Dis. 2011;29:215-21.

10. Hungin AP et al. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40 000 subjects. Aliment Pharm Ther. 2003;17:643-50.

11. Ringel Y et al. Effect of abuse history on pain reports and brain responses to aversive visceral stimulation: an FMRI study. Gastroenterology. 2008;134:396-404.

12. Elsenbruch S et al. Affective disturbances modulate the neural processing of visceral pain stimuli in irritable bowel syndrome: an fMRI study. Gut. 2010;59:489-95.

13. Lea R, Whorwell PJ. Quality of life in irritable bowel syndrome. Pharmacoeconomics. 2001;19:643-53.

14. Longstreth GF et al. Irritable bowel syndrome, health care use, and costs: a U.S. managed care perspective. Am J Gastroenterol. 2003;98:600-7.

15. Seres G et al. Different associations of health related quality of life with pain, psychological distress and coping strategies in patients with irritable bowel syndrome and inflammatory bowel disorder. J Clin Psychol Med Settings. 2008;15:287-95.

16. Bengtsson M et al. Anxiety in close relationships is higher and self-esteem lower in patients with irritable bowel syndrome compared to patients with inflammatory bowel disease. Eur J Intern Med. 2013;24:266-72.

17. Dupy H. The psychological general well-being (PGWB) index. Wenger NK, Mattson ME, Furberg CF, Elinson J (eds.), Assessment of quality of life in clinical trails of cardiovascular therapies (1984). New York: Le Jacq Publishing.

18. Dimenäs E et al. Well-being and gastrointestinal symptoms among patients referred to endoscopy owing to suspected duodenal ulcer. Scand J Gastroenterol. 1995;30:1046-52.

19. Drossman DA et al. A focus group assessment of patient perspectives on irritable bowel syndrome and illness severity. Dig Dis Sci. 2009;54:1532-41.

20. Farup PG et al. The symptomatic effect of cisapride in patients with irritable bowel syndrome and constipation. Scand J Gastroenterol. 1998;33:128-31.

21. McDowell I, Newell C. Measuring Health: A Guide to Rating Scales and Questionnaires (2nd ed.). New York, NY: Oxford University Press 1996.

22. Huskisson EC. Measurement of pain. J Rheumatol.1982;9:768-69.

23. Bengtsson M et al. Development and psychometric testing of the visual analogue scale for irritable bowel syndrome (VAS-IBS). BMC Gastroenterol. 2007;7:16.

24. Bengtsson M et al. Further validation of the visual analogue scale for irritable bowel syndrome (VAS-IBS) after use in clinical practice. Gastroenterol Nurs. 2013;36:188-98.

25. Bengtsson M, Ohlsson B. The brief VAS-IBS questionnaire can be used to evaluate psychological well-being in patients with irritable bowel syndrome. Eur J Internal Med. 2013;24:e82-3. doi: 10.1016/j.ejim.2013.05.013. Epub 2013 Jun 15

26. Schmitt DP, Allik J. Simultaneous administration of the Rosenberg Self-Esteem Scale in 53 nations: exploring the universal and culture-specific features of global self-esteem. J Pers Soc Psychol. 2005;89:623-42.

27. Eriksson M, Lindström B. Validity of Antonovsky's sense of coherence scale: a systematic review. J Epidem Comm Health. 2005;59:460-6.

28. Olssøn I et al. The Norwegian version of the experiences in close relationships measure of adult attachment: Psychometric properties and normative data. Nord J Psychiatry. 2010;64:340-9.

29. Bengtsson M et al. Evaluation of gastrointestinal symptoms in different groups using the visual analogue scale for irritable bowel syndrome (VAS-IBS). BMC Gastroenterology. 2011;11:122.

30. Jeffery IB et al. The microbiota link to irritable bowel syndrome: an emerging story. Gut Microbes. 2012;3:572-6.

31. Ohlsson B et al. Functional bowel symptoms and GnRH Antibodies: common findings in patients with primary Sjögren´s syndrome but not in systemic sclerosis. Scand J Rheumatol. 2009;38:391-3.

32. Grover M, Drossman DA. Pain management in IBD. Inflamm Bowel Dis Monit. 2009;10:1-10.

33. Wingate D et al. Disorders of gastrointestinal motility: towards a new classification. J Gastroen-terol Hepatol. 2002;17 Suppl:S1-14.

34. Roth B, Ohlsson B. Gastrointestinal symptoms and psychological well-being in patients with microscopic colitis. Scand

J Gastroenterol. 2013;48:27-34.

35. Halpert A, Godena E. Irritable bowel syndrome patients' perspectives on their relationships with healthcare providers. Scand I Gastroenterol. 2011;46:823-30.

36. Dhaliwal SK, Hunt RH. Doctor-patient interaction for irritable bowel syndrome in primary care: a systematic perspective. Eur J Gastroenterol Hepatol. 2004;16:1161-6.

37. O´Sullivan MA et al. Patient knowledge and educational needs in irritable bowel syndrome. Eur J Gastroenterol Hepatol. 2000;12:39-43.

38. Francis CY et al. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. Aliment Pharm Ther. 1997;11:395-402.

39. McKenzie YA et al; Gastroenterology Specialist Group of the British Dietetic Association. British Dietetic Association evidence-based guidelines for the dietary management of irritable bowel syndrome in adults. J Hum Nutr Diet. 2012;25:260-74.

40. Asare F et al. Meditation over medication for irritable bowel syndrome? On exercise and alternative treatments for irritable bowel syndrome. Curr Gastroenterol Rep. 2012;14:283-9.

41. Farhadi A et al. Irritable bowel syndrome: an update on therapeutic modalities. Expert Opin Investig Drugs. 2001;10:1211-22.

ENDOSCOPIC OPTICAL ENHANCEMENT TECHNOLOGIES IN IBD

Gian Eugenio Tontini,[1,2] Maurizio Vecchi,[2,3] Markus F. Neurath,[1] Helmut Neumann[1]

1. Department of Medicine I, University of Erlangen-Nuremberg, Germany
2. Gastroenterology and Digestive Endoscopy Unit, IRCCS Policlinico San Donato, San Donato Milanese, Italy
3. Department of Biomedical Science for Health, University of Milan, Italy

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ABSTRACT

Optical enhancement technologies are emerging as promising tools to improve diagnosis and clinical management of patients with inflammatory bowel diseases (IBD). The use of dye-based and dye-less chromoendoscopy may improve either characterisation of mucosal inflammation or detection of dysplastic and early neoplastic lesions. Confocal laser endomicroscopy and endocytoscopy both allow for *in vivo* and real-time microscopic analysis of the tissue. Moreover, the newly introduced molecular imaging has now also become feasible for *in vivo* diagnosis in IBD. This review focuses on the more recent progresses of advanced endoscopic imaging techniques in the setting of IBD and provides the reader with an updated overview on accepted clinical evidence and ongoing fields of research.

Keywords: Inflammatory bowel disease, Crohn's disease, ulcerative colitis, colonoscopy, advanced endoscopic imaging, dye-based chromoendoscopy, dye-less chromoendoscopy, confocal laser endomicroscopy, molecular imaging, endocytoscopy, surveillance, colorectal cancer.

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC), the two major entities of inflammatory bowel disease (IBD), are gastrointestinal chronic disorders that affect more than 1 million people in the United States and several million worldwide.[1,2] The intestinal mucosal layer is the main target of such disorders and represents the environment where exogenous and host related factors mould the immunological background that bears IBD pathogenesis. Accordingly, endoscopic imaging has a pivotal role for both diagnostic and therapeutic issues in patients with IBD. Indeed, the differential diagnosis among IBD entities and other gastrointestinal disorders is based on clinical evaluation and the combination of endoscopic, histological, radiologic, and biochemical results.[3-9] Moreover, patients with either CD or UC are at an increased risk of malignancies as severity, extent, and standing of chronic inflammation are recognised as the major risk factors of colitis-associated cancer (CAC).[10-12] Therefore, national and international guidelines strongly recommend colonoscopic surveillance protocols starting 8-10 years after the onset of symptoms, and every 1 to 2 years after that in extensive colitis.[5,13-16] This strategy is aimed at early detection of non-polypoid and early dysplastic lesions, which are the most reliable biomarker of concomitant or impending malignancy.[17,18] In 2005, an international consensus conference agreed that a minimum of 32 biopsies should be performed at each surveillance colonoscopy by obtaining four-quadrant biopsies every 10 cm separately retrieved, plus targeted sampling of macroscopically suspicious lesions.[16] However, this approach has raised several concerns as it failed to show concrete cost-effectiveness and to cut down the risk of overlooked neoplastic lesions.[11,18-27]

Consistently, growing efforts have been made to improve the efficacy of advanced endoscopic imaging techniques during endoscopic surveillance protocols.[26-33] In addition, emerging evidence has raised increasing attention to a new clinical topic, namely mucosal healing. This includes the precise staging of disease extent and activity, and the mucosal early response to biological therapy.[34,35] In this context, advanced endoscopic imaging techniques could refine our traditional approach of diagnosis in patients with IBD and may become the crucial diagnostic test for more disease-specific and patient-centred clinical strategies.[36,37] This review describes the concept of advanced endoscopic imaging for diagnosis and characterisation of patients with IBD, focusing on the newly introduced optical enhancement technologies.

CHROMOENDOSCOPY

Chromoendoscopy uses different staining techniques to enhance the mucosal detail and submucosal vascular pattern, thereby improving the detection of pathological lesions and enabling a more precise diagnosis.[28,36-38] Currently, chromoendoscopy is distinguished in dye-based and dye-less imaging techniques.

Dye-Based Chromoendoscopy

Dye-based chromoendoscopy (DBC) refers to topical application of dyes at the time of endoscopy in an effort to enhance tissue characterisation, differentiation, and diagnosis.[39] Dye spraying techniques were first described in the 1970s[40] and include absorptive agents (e.g. Lugol's solution, methylene blue, toluidine blue, and cresyl violet), contrast agents (e.g. indigo carmine and acetic acid), and reactive staining agents (e.g. congo red and phenol red).[28,41] DBC may allow for an improved diagnosis of disease severity and extent in subjects with IBD. Nevertheless, DBC has been implemented in clinical practice specially to improve detection of dysplastic lesions in long-standing IBD colitis.[21,42-47] In this context it has been estimated that methylene blue-aided chromoendoscopy yields a 2.2-fold increased dysplasia detection rate, particularly due to the enhanced detection of non-polypoid lesions.[21,47,48] Similar results have also been shown for indigo carmine-aided chromoendoscopy;[43,46] moreover, indigo carmine has no oxidative damage on DNA chains, thereby theoretically avoiding the potential carcinogenic effect ascribed to the prolonged use of methylene-blue under white-light scanning.[49-52] A meta-analysis of six randomised controlled trials demonstrated a pooled sensitivity, specificity and diagnostic odds ratio of 83.3% (95%-CI=35.9-99.6%), 91.3% (95%-CI=43.8-100%), and 17.5% (95%-CI=1.2-247.1), respectively, for dysplasia detection in long-standing UC by using DBC compared with white-light endoscopy.[53] Accordingly, international guidelines have included the use of DBC in highly specialised centres to improve IBD surveillance protocols [4,13-16]. Potential limitations that could hamper the use of DBC in clinical practice include additional costs for the dye and the spraying catheter, operator training, and a non-uniform distribution on the mucosal surface.[28,33-37] Furthermore, there is no dye that provides a detailed evaluation of the mucosal vascular pattern (MVP), which is nowadays emerging as an important parameter for neoplasia detection and assessment of disease activity. [37]

Dye-Less Chromoendoscopy

Recently, dye-less chromoendoscopy (DLC) techniques have been implemented into daily routine practice to overcome the above-mentioned limitations of DBC. By pushing a button on the handle of the endoscope, these integrated endoscopic systems enable a detailed examination of both the mucosal surface and the MVP morphology, thereby providing high-contrast imaging in real-time and without the use of additional equipment. DLC encompasses optical chromoendoscopy and digital chromoendoscopy techniques.[37]

Optical chromoendoscopy techniques (Narrow Band Imaging or NBI, Olympus, Tokyo, Japan and Compound Band Imaging or CBI, Aohua, Shanghai, China) are based on optical lenses integrated within the light source of the endoscope, which narrow the bandwidth of spectral transmittance.[54] In contrast, digital chromoendoscopy (Fujinon Intelligent Color Enhancement or FICE, Fujifilm, Tokyo, Japan and i-scan, Pentax, Tokyo, Japan) rests on a digital post-processing of endoscopic images made in real-time by the video processor.[37]

As formerly discussed, detection of colorectal dysplasia in IBD is of paramount importance, being the most reliable biomarker of CAC.[17,18]

Consistently, several studies have recently addressed the potential of DLC, particularly NBI, in improving the accuracy and effectiveness of current surveillance programs in IBD. In a crossover randomised trial in which patients with UC underwent both NBI and high-definition (HD) white-light colonoscopy, van den Broek and co-workers[55] have found that NBI does not improve the detection of neoplastic lesions. In addition, NBI proved the suboptimal accuracy (73%) for differentiating neoplastic from non-neoplastic mucosa.[55] A further study by the same group confirmed that NBI has only a moderate accuracy for the prediction of histology (80%).[56]

Another prospective, randomised, crossover trial compared NBI to DBC with indigo carmine in 60 clinically inactive IBD patients 8 years after the onset of symptoms.[57] NBI detected significantly less false-positive biopsies, sparing time and yielding an equivalent true-positive rate. However, DBC scored slightly better than NBI identifying more neoplastic lesions and more neoplastic patients (p=0.2), thereby harbouring some concern about the use of this DLC technique as standard surveillance strategy in IBD.[56] Assessing the characterisation of early colorectal lesions in long-standing UC, Matsumoto et al.[58] combined NBI with magnification colonoscopy in a pilot study based on 46 patients. According to the modified classification for 'magnifying chromoscopic findings' the surface pattern of each lesion was defined as 'honeycomb-like', 'villous' or 'tortuous-like'. Dysplasia was positively correlated with the 'tortuous' pattern, therefore suggesting that NBI and magnified colonoscopy could improve dysplasia detection during surveillance in UC.[58] To the best of our knowledge, there are no studies on the use of digital chromoendoscopy techniques (i.e. i-scan and FICE) for detection and characterisation of intraepithelial neoplasia in IBD.

More recently, DLC techniques have shown promising results for the characterisation of disease extent and activity in patients with mild or inactive IBD.[37,59] Kudo et al.[60] have focused their analysis on MVP comparing HD white-light endoscopy and NBI in UC patients by using histology as the reference standard. NBI was able to better characterise abnormal vessel structures, distinguishing between 'clear' and 'obscure' MVP where HD white-light endoscopy identified only a common 'distorted' MVP. Histopathology revealed that both acute and chronic signs of microscopic inflammation were remarkably correlated with the 'obscure' MVP ($p<0.05$), while only few signs of chronic inflammation correlated with the 'distorted and clear' MVP.[60] Additional research from the same group confirmed that MVP's analysis with NBI offers the concrete possibility to predict signs of acute microscopic inflammation in patients with quiescent UC.[60-63]

Very recently, our group evaluated the potential of i-scan to improve the characterisation of mucosal inflammation in IBD.[64] During pancolonoscopy, patients were examined using both HD white-light (Group A) and HD plus i-scan (Group B). Agreement between endoscopic prediction of disease severity and histological findings was 54% in group A and 90% in group B (p=0.066). The endoscopic prediction of the inflammatory activity's extent was 49% in group A and 92% in group B (p=0.001) using histology as reference standard, thereby suggesting that i-scan has the potential to improve both diagnosis of severity and extent of mucosal inflammation in patients with IBD. Therefore, this allows for a more precise diagnosis of mucosal inflammation compared to HD colonoscopy alone.[64] Taken together, even if DBC still represents the best choice to improve dysplasia detection in long-standing IBD, optical and digital DLC techniques have the potential to better quantify disease activity and mucosal healing, and currently appear as more practical tools to spread into daily routine clinical practice.

CONFOCAL LASER ENDOMICROSCOPY

Introduced in 2004, confocal laser endomicroscopy (CLE) has rapidly emerged as a promising approach to obtain real-time *in vivo* histology in luminal endoscopy as in several other clinical fields.[65] Briefly, this technique is based on tissue illumination with a blue laser light after topical or systemic application of fluorescence agents. In IBD, various studies have investigated the potential of CLE for disease classification and characterisation.[21,35,66-76]

In 2007, a study from Kiesslich et al.[21] clearly demonstrated that during surveillance of long-standing UC, the use of DBC-aided CLE

could detect 4.75-fold more neoplastic lesions compared with standard white-light endoscopy. In addition, the authors reported a remarkable biopsy sparing and an optimal accuracy (95%) in predicting the presence of neoplastic changes.[21] Consistent with this figure, Hurlstone and co-workers[76] described a high overall accuracy (97%) and excellent agreement with histological results (*κappa*=0.91) when using CLE for differentiation of dysplasia-associated lesion or mass (DALM) from sporadic adenoma (adenoma-like mass; ALM).

Beyond the characterisation of dysplastic changes, confocal imaging could also reveal signs of impaired intestinal barrier function, which is emerging as a crucial step in the pathogenesis of IBD.[68,73,74,77-82] The lining of the intestine undergoes a continuous renewal, resulting in epithelial gaps as a consequence of intestinal cell shedding.[68] A refined process, based on the redistribution of tight junction round the basolateral surface of the shed cell, preserves the barrier function at the gap site.[74] When this physiologic process is impaired, the intestinal barrier become permeable to the inward flow of antigens and microbes from the intestinal lumen into the bowel wall, paving the way to a prompt reaction of the immune system.[78] Accordingly, it has been hypothesised that the rate of epithelial cell shedding is increased in patients with IBD.[68] Recently, Liu et al.[69] have shown that CLE can be used to quantify *in vivo* the epithelial gap density of the terminal ileum during ongoing colonoscopy. They confirmed that epithelial gap density is significantly higher in IBD subjects than in negative controls. Nonetheless, ulcerative pancolitis and severe clinical disease were associated with lower gap densities compared with those observed in IBD with limited colitis and with mild-to-moderate clinical disease, thereby suggesting that gap density does not correlate with disease activity and neither with specific IBD entities.[69]

A further study by Kiesslich and co-workers[73] confirmed that CLE can identify cell shedding and barrier loss at a microscopic level in real-time. Employing a murine model of cell shedding, they also demonstrated that an incomplete sealing at the site of cell shedding ('gap') can result in either outward flow, inward flow or bidirectional flow. This finding supports the hypothesis that outward flow of fluorescein into the intestinal lumen identified by CLE is a marker of loss of barrier function, as it implies the inward flow of antigens, toxins and microbes activating the mucosal immune system. Furthermore, the authors developed a grading system ('Watson grade') based on three CLE signs of barrier function impairment such as cell shedding, fluorescein flow into the intestinal lumen, and microerosions. The 'Watson grade' was shown to predict the relapse of IBD patients in remission within the subsequent 12 months (Watson grade II/III versus grade I: $p<0.001$), harbouring the use of CLE for on demand *in vivo* prediction of relapse during ongoing endoscopy.[73] Another pilot study based on both CD and UC patients with a median follow-up of 14 months has recently confirmed that gap density in endoscopically normal mucosa of the terminal ileum is a significant predictor for risk of major events such as hospitalisation or surgery.[74]

Moreover, several studies have recently established that CLE allows the characterisation of most microscopic architectural and inflammatory changes, which are conventionally regarded as histopathological hallmarks for the diagnosis of IBD.[9,66-72] In a study published in 2012, our group evaluated the feasibility of CLE for *in vivo* microscopic diagnosis of disease severity in patients with CD.[72] Consistent with histopathological results, CLE showed a sharp distinction between CD and controls based on different rates of the following findings: crypt morphology (number of colonic crypts, crypt tortuosity, crypt lumen), microerosions, vascularity, cellular infiltrate within the lamina propria and number of goblet cells. In addition, CLE was able to differentiate quiescent from active CD showing a high rate of crypt atrophy in the former group, as well as control subjects from quiescent CD, detecting a significant increase in crypt and goblet cell number as hallmarks of chronic inflammation.[72] Similar results were also shown in another study based on the use of CLE in patients suffering from UC.[71] Both assessment of crypt architecture (irregular arrangement, density, dilation, abscess) and fluorescein leakage into the crypt lumen with CLE showed good correlations with histological results (both $p<0.001$). Moreover, 57% of patients with normal mucosa seen on conventional white-light endoscopy (Baron score=0) showed acute inflammation on histology (Geboes index >3), whereas no patients with normal mucosa or

with chronic inflammation seen on CLE showed acute inflammation on histology.

In recent years, CLE has been integrated with the use of exogenous fluorescently labelled probes to specifically highlight neoplastic and inflammatory changes on the basis of their molecular signature; this novel and promising field in gastroenterology is called 'molecular imaging'.[8] In a pilot study, Atreya and co-workers[35] used CLE-based molecular imaging with monoclonal anti-tumour necrosis factor (TNF) antibodies to evaluate whether the therapeutic responses to Adalimumab correlate with the amount of mucosal membrane TNF receptor in patients with CD. The inflamed mucosa was coated with a newly developed fluorescent anti-TNF antibody (FITC-Adalimumab) during the colonoscopy prior to anti-TNF therapy. Fluorescein expression on a cellular level was quantified by CLE analysis focused on mucosal membrane-bound TNF+ (mTNF+) cells. During a follow-up period of 1 year, patients with a great density of mTNF+ cells showed significantly higher short-term response rates at week 12 (92%) upon subsequent anti-TNF therapy as compared to patients with low amounts of mTNF+ cells (15%). These data indicate for the first time that *in vivo* molecular imaging with fluorescent antibodies is feasible and safe, and could predict therapeutic responses to biological treatment, depicting promising and immediate potential for translational science and prompting effects on clinical practice.[35]

Multiphoton microscopy (MPM) is emerging as one of the most important *in vivo* imaging techniques for basic research. In comparison with the single photon excitation performed by CLE, MPM uses nonlinear optics, so that various molecular components can be discriminated without the need to apply fluorophores. The result is a superior effective resolution in thick tissue samples and an increased penetration depth, with images perfectly suited for the acquisition in 3D.[84] One recent article impressively demonstrated how MPM allows for a well-defined 3D visualisation of pathologic changes in tissue samples from patients with IBD without requiring exogenous fluorophores.[85]

Taken together, CLE appears as a versatile tool capable of enriching the power of endoscopy, predicting *in vivo* both several valuable cues of histology and the response rate to anti-TNF therapy. However, currently CLE is relatively expensive and time-consuming, therefore harbouring potential shortcomings that currently limit its implementation into daily routine clinical practice.

ENDOCYTOSCOPY

Endocytoscopy (EC) is another advanced imaging technique implemented for *in vivo* microscopic imaging at a magnification up to 1390-fold.[86] Based on the principle of contact light microscopy, this technique enables the visualisation of the very superficial mucosal layer at a cellular and subcellular level.[87] EC has recently been evaluated in gastrointestinal endoscopy, particularly to detect neoplastic changes in aberrant crypt foci and to differentiate neoplastic from non-neoplasic colorectal lesions.[88-90] Our group has recently published the results of a pilot study designed to assess the feasibility of EC in distinguishing single inflammatory cells in patients with IBD.[91] It has been observed that EC enables a sharp characterisation of several cellular (cell size, arrangement and density) and subcellular details (size and shape of nuclei and nucleus-to-cytoplasm ratio). Consistently, EC could reliably distinguish different inflammatory cells with the following respective sensitivities and specificities: neutrophilic (60% and 95%), basophilic (74% and 94%), eosinophilic granulocytes (75% and 91%), and lymphocytes (89% and 93%). Furthermore, intestinal disease activity assessed by EC was perfectly in agreement with histopathological results (100%).[91] Taken together, these data seem to nominate EC as a new promising method to characterise and assess the severity of mucosal inflammation in IBD.

CONCLUSION

Recent technological advances in optical imaging and luminal endoscopy are greatly improving the quality of gastrointestinal imaging, enabling microscopic and molecular analysis in real-time during ongoing endoscopy. Converging lines of evidence suggest many promising applications of these optical advanced imaging techniques in several IBD clinical settings. DLC is emerging as a practical method to enhance in real-time mucosal subtle details, thereby potentially improving the detection and characterisation of dysplastic lesions, as well as the accuracy in assessing disease activity and extent. CLE and EC allow

for real-time *in vivo* histology during ongoing endoscopy with predictable benefits for diagnosis and surveillance of IBD subjects. The newly introduced molecular imaging can even overcome the limits of traditional morphological analysis, driving the endoscopic imaging towards the quantification of specific biochemical processes, thereby promoting the examination of functional data. However, further clinical studies are still required to assess the cost-effectiveness and the best strategies for the correct use of these optical enhanced techniques in clinical practice.

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REFERENCES

1. Abraham C, Cho JH. Inflammatory bowel disease. N Engl J Med. 2009;361(121):2066-78.

2. Cominelli F. Inhibition of leukocyte trafficking in inflammatory bowel disease. N Engl J Med. 2013;369(8):775-6.

3. Dignass A et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. J Crohns Colitis. 2012;6(10):965-90.

4. Annese V et al. European evidence based consensus for endoscopy in inflammatory bowel disease. J Crohns Colitis. 2013;7(12):982-1018.

5. Van Assche G et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 3: special situations. J Crohns Colitis. 2013;7(1):1-33.

6. Mowat C et al. Guidelines for the management of inflammatory bowel disease in adults. Gut. 2011;60(5):571-607.

7. Lichtenstein GR et al. Practice Parameters Committee of American College of Gastroenterology. Management of Crohn's disease in adults. Am J Gastroenterol. 2009;104(2):465-83.

8. Kornbluth A, Sachar DB, Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 2010;105(3):501-23. Erratum in Am J Gastroenterol. 2010;105(3):500.

9. Magro F et al. European consensus on the histopathology of inflammatory bowel disease. J Crohns Colitis. 2013;7(10):827-51.

10. Eaden JA et al. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut. 2001;48:526-35.

11. Collins PD et al. Strategies for detecting colon cancer and/or dysplasia in patients with inflammatory bowel disease. Cochrane Database Syst Rev. 2006;2:CD000279.

12. Ullman TA, Itzkowitz SH. Intestinal inflammation and cancer. Gastroenterology. 2011;140(6):1807-16.

13. Farraye FA et al. AGA technical review on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. Gastroenterology. 2010;138(2):746-74.

14. Cairns SR et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups. Gut. 2010;59:666-89.

15. Rex DK et al. American College of Gastroenterology guidelines for colorectal cancer screening 2009. Am J Gastroenterol. 2009;104(3):739-50.

16. Itzkowitz SH, Present DH. Consensus conference: Colorectal cancer screening and surveillance in inflammatory bowel disease. Inflamm Bowel Dis. 2005;11(3):314-21.

17. Goldmann H. Significance and detection of dysplasia in chronic colitis. Cancer. 1996;78(11):2261–3.

18. Rubin CE et al. DNA aneuploidy in colonic biopsies predicts future development of dysplasia in ulcerative colitis. Gastroenterology. 1992;103(5):1611-20.

19. Rutter MD et al. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. Gastroenterology. 2006;130(4):1030-8.

20. Leung K et al. Ongoing colorectal cancer risk despite surveillance colonoscopy: The Polyp Prevention Trial Continued Follow-up Study. Gastrointest Endosc. 2010;71(1):111–7.

21. Kiesslich R et al. Chromoscopy-guided endomicroscopy increases the diagnostic yield of intraepithelial neoplasia in ulcerative colitis. Gastroenterology. 2007;132(3):874-82.

22. Robertson DJ et al. Colorectal cancer in patients under close colonoscopic surveillance. Gastroenterology. 2005;129(1):34-41.

23. Rutter M et al. Endoscopic appearance of dysplasia in ulcerative colitis and the role of staining. Endoscopy. 2004;36(12):1109-14.

24. Ransohoff DF et al. Ulcerative colitis and colonic cancer. Problems in assessing diagnostic usefulness of mucosal dysplasia. Dis Colon Rectum. 1985;28(6):383-8.

25. Eaden JA et al. How gastroenterologists screen for colonic cancer in ulcerative colitis: an analysis of performance. Gastrointest Endosc. 2000;51(2):123-28.

26. Vienne A et al. Low prevalence of colonoscopic surveillance of inflammatory bowel disease patients with longstanding extensive colitis: a clinical practice survey nested in the CESAME cohort. Aliment Pharmacol Ther. 2011;34(2):188-95.

27. Ullman TA et al. Biopsy specimen numbers in the routine practice of surveillance colonoscopy in ulcerative colitis (UC).Gastroenterology. 2004;126:471.

28. Kiesslich R, Neurath MF. Chromoendoscopy in inflammatory bowel disease. Gastroenterol Clin North Am. 2012;41(2):291-302.

29. Bernstein CN. The color of the most effective tool to use in dysplasia surveillance in inflammatory bowel disease. Gastrointest Endosc. 2011;74(4):849-51.

30. Efthymiou M et al. Cancer surveillance strategies in ulcerative colitis: the need for modernization. Inflamm Bowel Dis. 2011;17(8):1800-13.

31. Bessissow T, Bisschops R. Advanced endoscopic imaging for dysplasia

surveillance in ulcerative colitis. Expert Rev Gastroenterol Hepatol. 2013;7(1):57-67.

32. Ullman TA. Chromoendoscopy should be the standard method and more widely used for cancer surveillance colonoscopy in ulcerative colitis. Inflamm Bowel Dis. 2007;13(10):1273-4.

33. Kiesslich R, Neurath MF. Chromoendoscopy: an evolving standard in surveillance for ulcerative colitis. Inflamm Bowel Dis. 2004;10(5):695-6.

34. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut. 2012;61(11):1619-35.

35. Atreya R et al. In vivo molecular imaging using fluorescent anti-TNF antibodies and confocal laser endomicroscopy predicts response to anti-TNF therapy in Crohn's disease patients. Nature Medicine 2013. [In press].

36. Neumann H et al. New endoscopic approaches in IBD. World J Gastroenterol. 2011;17(1):63-8.

37. Tontini GE et al. Review article: newer optical and digital chromoendoscopy techniques vs. dye-based chromoendoscopy for diagnosis and surveillance in inflammatory bowel disease. Aliment Pharmacol Ther. 2013; 38(10):1198-208.

38. Neumann H et al. Advanced endoscopic imaging for diagnosis of Crohn's disease. Gastroenterol Res Pract. 2012;2012:301541.

39. Wong Kee Song LM et al. ASGE Technology Committee. Chromoendoscopy. Gastrointest Endosc. 2007;66(4):639-49.

40. Tada M et al. On the dye spraying method in colonofibreoscopy. Endoscopy. 1977;8(2):70-4.

41. Canto MI. Staining in gastrointestinal endoscopy: the basics. Endoscopy. 1999;31(6):479-86.

42. Subramanian V et al. Meta-analysis: the diagnostic yield of chromoendoscopy for detecting dysplasia in patients with colonic inflammatory bowel disease. Aliment Pharmacol Ther. 2011;33(3):304-12.

43. Hurlstone DP et al. Indigo carmine-assisted high-magnification chromoscopic colonoscopy for the detection and characterisation of intraepithelial neoplasia in ulcerative colitis: a prospective evaluation. Endoscopy. 2005;37(12):1186-92.

44. Hurlstone DP et al. Further validation of high-magnification chromoscopic colonoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. Gastroenterology. 2004;126(1):376-8.

45. Marion JF et al. Chromoendoscopy-targeted biopsies are superior to standard colonoscopic surveillance for detecting dysplasia in inflammatory bowel disease patients: a prospective endoscopic trial. Am J Gastroenterol. 2008;103(9):2342-9.

46. Rutter MD et al. Pancolonic indigo carmine dye spraying for the detection of dysplasia in ulcerative colitis. Gut. 2004;53(2):256-60.

47. Kiesslich R et al. Methylene blue aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. Gastroenterology. 2003;124(4):880-8.

48. East JE et al. Magnification pan-chromoendoscopy remains the mainstay for colitis dysplasia detection and differentiation. Gastroenterology. 2007;133(1):366-7.

49. Olliver JR et al. Chromoendoscopy with methylene blue and associated DNA damage in Barrett's oesophagus. Lancet. 2003; 362(9381):373-4.

50. Hardie LJ et al. Chromoendoscopy with methylene blue and the risk of DNA damage. Gastroenterology. 2004;126(2):623; author reply 623-4.

51. Davies J et al. Methylene blue but not indigo carmine causes DNA damage to colonocytes in vitro and in vivo at concentrations used in clinical chromoendoscopy. Gut. 2007;56(1):155-6.

52. Dinis-Ribeiro M, Moreira-Dias L. There is no clinical evidence of consequences after methylene blue chromoendoscopy. Gastrointest Endosc. 2008;67(7):1209.

53. Wu L et al. The diagnostic accuracy of chromoendoscopy for dysplasia in ulcerative colitis: meta-analysis of six randomized controlled trials. Colorectal Dis. 2012;14(4):416-20.

54. Kuznetsov K et al. Narrow–band imaging: potential and limitations. Endoscopy. 2006;38(1):76-81.

55. van den Broek FJ et al. Narrow-band imaging versus high-definition endoscopy for the diagnosis of neoplasia in ulcerative colitis. Endoscopy. 2011;43(2):108-15.

56. van den Broek FJ et al. Endoscopic tri-modal imaging for surveillance in ulcerative colitis: randomised comparison of high-resolution endoscopy and autofluorescence imaging for neoplasia detection; and evaluation of narrow-band imaging for classification of lesions. Gut. 2008;57(8):1083-9.

57. Pellisé M et al. Narrow-band imaging as an alternative to chromoendoscopy for the detection of dysplasia in long-standing inflammatory bowel disease: a prospective, randomized, crossover study. Gastrointest Endosc. 2011;74(4):840-8.

58. Matsumoto T et al. Magnifying colonoscopy with narrow band imaging system for the diagnosis of dysplasia in ulcerative colitis: a pilot study. Gastrointest Endosc. 2007;66(5):957-65.

59.Tontini GE et al. Advanced endoscopic imaging techniques in Crohn's disease. J Crohns Colitis 2013;doi:10.1016/j.crohns.2013.09.004. [Epub ahead of print].

60. Kudo T et al. Mucosal vascular pattern in ulcerative colitis: observations using narrow band imaging colonoscopy with special reference to histologic inflammation. Int J Colorectal Dis. 2009;24(5):495-501.

61. Matsumoto T et al. Magnifying NBI colonoscopic findings in ulcerative colitis. Stomach Intestine. 2007;42:877-81.

62. Matsumoto T et al. Autofluorescence imaging colonoscopy in ulcerative colitis: comparison with conventional and narrow-band imaging colonoscopy. Dig Endosc. 2007;19:139-44.

63. Esaki M et al. Endoscopic findings under narrow band imaging colonoscopy in ulcerative colitis. Dig Endosc. 2011;1:140-2.

64. Neumann H et al. Virtual chromoendoscopy for prediction of severity and disease extent in patients with inflammatory bowel disease: a randomized controlled study. Inflamm Bowel Dis. 2013;19(9):1935-42.

65. Neumann H et al. Confocal laser endomicroscopy: technical advances and clinical applications. Gastroenterology. 2010;139(2):388-92.

66. Watanabe O et al. Confocal endomicroscopy in patients with ulcerative colitis. J Gastroenterol Hepatol. 2008;2:S286-90.

67. Krauss E et al. Characterization of lymphoid follicles with red ring signs as first manifestation of early Crohn's disease by conventional histopathology and confocal laser endomicroscopy. Int J Clin Exp Pathol. 2012;5(5):411-21.

68. Liu JJ et al. Mind the gaps: confocal endomicroscopy showed increased density of small bowel epithelial gaps in inflammatory bowel disease. J Clin Gastroenterol. 2011;45(3):240-5.

69. Liu JJ et al. Increased epithelial gaps in the small intestines of patients with inflammatory bowel disease: density matters. Gastrointest Endosc. 2011;73(6):1174-80.

70. Trovato C et al. Confocal laser endomicroscopy for the detection of mucosal changes in ileal pouch after restorative proctocolectomy. Dig Liver Dis. 2009;41(8):578-85.

71. Li CQ et al. Classification of inflammation activity in ulcerative colitis by confocal laser endomicroscopy. Am J Gastroenterol. 2010;105(6):1391-6.

72. Neumann H et al. Assessment of Crohn's disease activity by confocal laser endomicroscopy. Inflamm Bowel Dis.

2012;18(12):2261-9.

73. Kiesslich R et al. Local barrier dysfunction identified by confocal laser endomicroscopy predicts relapse in inflammatory bowel disease. Gut. 2012;61(8):1146-53.

74. Turcotte JF et al. Increased epithelial gaps in the small intestine are predictive of hospitalization and surgery in patients with inflammatory bowel disease. Clin Transl Gastroenterol. 2012;3:e19.

75. van den Broek FJ et al. Pilot study of probe-based confocal laser endomicroscopy during colonoscopic surveillance of patients with longstanding ulcerative colitis. Endoscopy. 2011;43(2):116-22.

76. Hurlstone DP et al. Confocal endomicroscopy in ulcerative colitis: differentiating dysplasia-associated lesional mass and adenoma-like mass. Clin Gastroenterol Hepatol. 2007;5(10):1235-41.

77. Su L et al. TNFR2 activates MLCK-dependent tight junction dysregulation to cause apoptosis-mediated barrier loss and experimental colitis. Gastroenterology. 2013;145(2):407-15.

78. Salim SY, Söderholm JD. Importance of disrupted intestinal barrier in inflammatory bowel diseases. Inflamm Bowel Dis. 2011;17(1):362-81.

79. Meddings J. The significance of the gut barrier in disease. Gut. 2008;57(4):438e40.

80. Wyatt J et al. Intestinal permeability and the prediction of relapse in Crohn's disease. Lancet. 1993;341:1437e9.

81. Marchiando AM et al. The epithelial barrier is maintained by in vivo tight junction expansion during pathologic intestinal epithelial shedding. Gastroenterology. 2011;140(4):1208e18.

82. Su L et al. Targeted epithelial tight junction dysfunction causes immune activation and contributes to development of experimental colitis. Gastroenterology. 2009;136(2):551-63.

83. Atreya R, Goetz M. Molecular imaging in gastroenterology. Nat Rev Gastroenterol Hepatol. 2013;doi: 10.1038/nrgastro.2013.125. [Epub ahead of print].

84. Zipfel WR et al. Nonlinear magic: multiphoton microscopy in the biosciences. Nat Biotechnol. 2003;21(11):1369-77.

85. Schürmann S et al. Label-free imaging of inflammatory bowel disease using multiphoton microscopy. Gastroenterology. 2013;145(3):514-6.

86. Neumann H et al. Review article: in vivo imaging by endocytoscopy. Aliment Pharmacol Ther. 2011;33(11):1183-93.

87. Neumann H, Kiesslich R. Endomicroscopy and endocytoscopy in IBD. Gastrointest Endosc Clin N Am. 2013;23(3):695-705.

88. Pohl H et al. Endocytoscopy for the detection of microstructural features in adult patients with celiac sprue: a prospective, blinded endocytoscopy-conventional histology correlation study. Gastrointest Endosc. 2009;70(5):933-41.

89. Cipolletta L et al. Endocytoscopy can identify dysplasia in aberrant crypt foci of the colorectum: a prospective in vivo study. Endoscopy. 2009;41(2):129-32.

90. Neumann H et al. Image of the month. Endocytoscopy-based detection of focal high-grade intraepithelial neoplasia in colonic polyps. Clin Gastroenterol Hepatol. 2011;9(2):e13.

91. Neumann H et al. Endocytoscopy allows accurate in vivo differentiation of mucosal inflammatory cells in IBD: a pilot study. Inflamm Bowel Dis. 2013;19(2):356-62.

ADHESION MOLECULES AS A THERAPEUTIC TARGET IN IBD

Raquel F. Leal, Azucena Salas

Institut d'investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Center Esther Koplowitz, Barcelona, Spain

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ABSTRACT

Recruitment of circulating leukocytes to areas of inflammation is a key process in the pathophysiology of inflammatory bowel diseases, including ulcerative colitis (UC). This is a finely regulated multistep process in which specialised adhesion and signalling molecules mediate a series of sequential steps. Following activation, integrins expressed on the surface of leukocytes become the key mediators of firm adhesion and emigration through interaction with immunoglobulin superfamily molecules expressed on the vascular endothelium. The anti α4 antibody natalizumab has shown efficacy in inducing and maintaining response and remission in patients with moderate and severe Crohn's disease. However, a major safety setback involving the onset of progressive multifocal leukoencephalopathy (PML) in 1/1000 treated cases led to limitations on its clinical use and application in UC. The more selective anti α4β7 antibody vedolizumab has proven efficacious for inducing clinical and endoscopic remission in UC. Selective expression of the α4β7 receptor MAdCAM-1, which occurs predominantly in the intestine, may avoid the risk of those central nervous system infectious complications associated with the nonselective blockade of all α4 integrins. Moreover, treatment with anti-MAdCAM-1 or anti-α7 antibody (etrolizumab) showed promising results for inducing remission in UC. In conclusion, the development of safe and effective drugs that target these molecular components of the inflammatory response may yield novel, improved therapies for inflammatory bowel disease (IBD) that address as yet unmet needs.

Keywords: Adhesion molecules, inflammatory bowel disease, ulcerative colitis, integrins, natalizumab, vedolizumab, etrolizumab, MAdCAM-1.

INTRODUCTION

The hallmark of ulcerative colitis (UC) lesions is infiltration of the intestine by mononuclear cells, predominantly lymphocytes. This cellular infiltration is the result of increased leukocyte recruitment and proliferation in the inflamed organ, together with a decrease in apoptosis. Adhesion molecules are cell surface-expressed glycoproteins that mediate cell-cell and cell-extracellular matrix interactions. Apart from playing a prominent role in leukocyte recruitment, they mediate important interactions with extracellular components that determine the survival and activation of immune cells. Adhesion molecules therefore represent promising therapeutic targets for human inflammatory diseases, including UC.[1]

Some of the current challenges now hindering the development of effective and safe anti-adhesion drugs for inflammatory bowel disease (IBD) therapy include identification of the most relevant, but selective, targets that predominantly affect recruitment to the inflamed intestine while preserving immune surveillance in other organs.

LEUKOCYTE-ENDOTHELIAL CELL INTERACTIONS

Leukocyte recruitment is initiated by their interaction with the blood vascular endothelium, primarily within specialised postcapillary venules. This interaction between circulating leukocytes and venular endothelium involves a multistep process in which specialised adhesion and

signalling molecules participate in mediating each of a series of sequential steps. In the first step, leukocytes marginalised from the central venular blood flow make contact with the endothelium and initiate rolling along the vascular lumen. This rolling delays the transit of leukocytes and allows 'sampling' of the local microenvironment for potential activating factors (chemokines) expressed on endothelial cells. Activation of leukocytes through this interaction with chemokines constitutes the second step of leukocyte recruitment. Chemokines bind to serpentine receptors and trigger rapid intracellular signalling in leukocytes, leading to functional activation of cell-surface adhesion molecules (integrins) through conformational changes that facilitate cell arrest on the vessel wall. This firm arrest is also favoured by cytokine-induced upregulation of binding receptors on endothelial cells. The final step, known as transendothelial leukocyte migration, is similarly orchestrated by chemotactic gradients stemming from the perivascular compartment (Figure 1).[2] Each stage of leukocyte recruitment - i.e. rolling, firm adhesion, and transendothelial migration - involves the participation of different families of adhesion molecules, including the selectins and their ligands, integrins, and the immunoglobulin superfamily.

INTEGRINS, THEIR RECEPTORS, AND THEIR INVOLVEMENT IN LEUKOCYTE RECRUITMENT

Integrins are heterodimeric proteins consisting of non-covalently associated α and β subunits. Leukocytes can express 13 different integrins from the existing repertoire.[3] Six different integrins contain the β_1 (CD29), β_2 (CD18), or β_7 subunits and serve as key mediators of leukocyte-endothelial cell adhesion. Their expression patterns and ligand partners vary among leukocyte populations (Table 1).

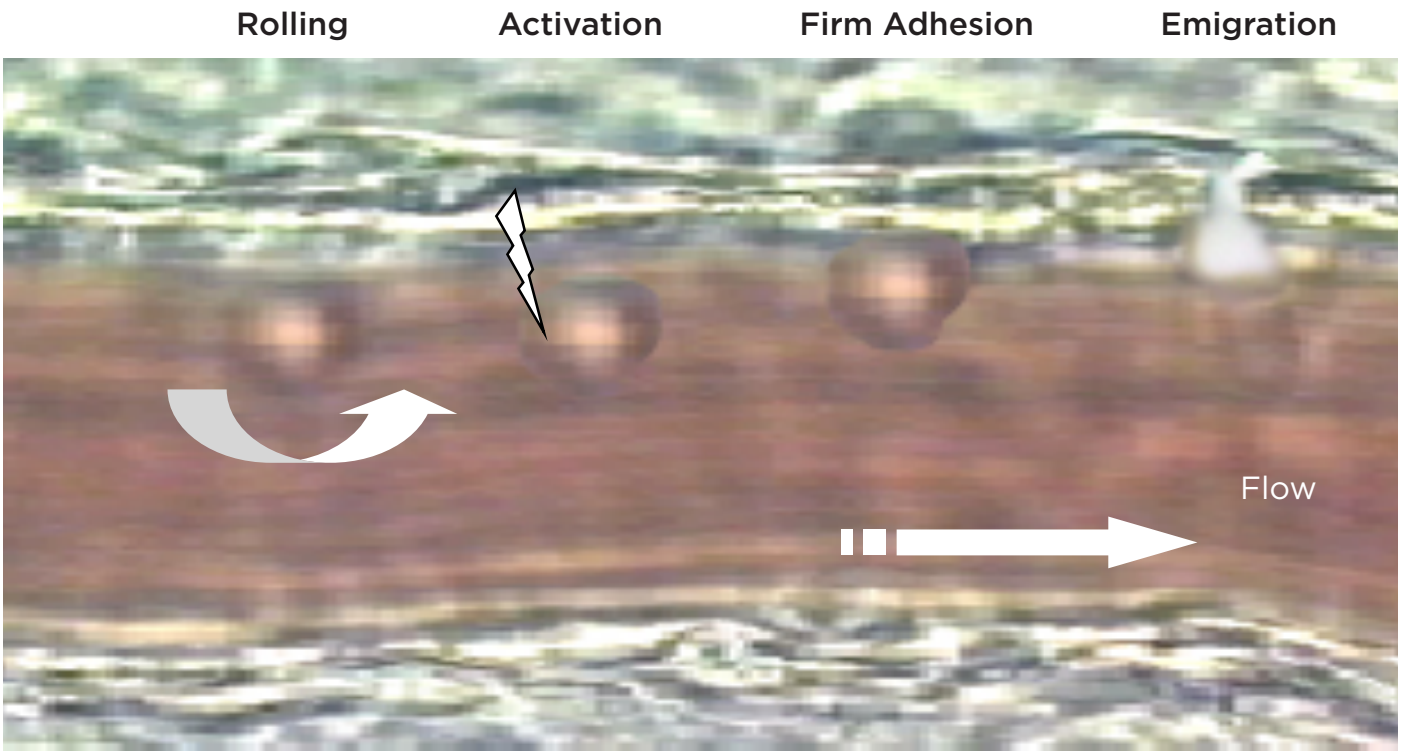

Figure 1. Steps of leukocyte recruitment.
Leukocyte-endothelial cell interactions. Schematic of the multistep model of leukocyte-endothelial cell adhesion. Fast moving leukocytes in the blood stream roll on activated endothelium via interactions between selectins and their ligands, or in some cases among integrin (α4)-immunoglobulin superfamily (MAdCAM-1) interactions. Selectins mediate the initial tethering and rolling interactions. Interactions between integrins and immunoglobulin superfamily members mediate firm adhesion and transmigration.

Table 1. Integrins and their receptors.

Adhesion Molecule	Location	Expression		Ligand	Function
		Constitutive	Inducible		
Integrin family					
CD11a/CD18 (LFA-1, $\alpha_L\beta_2$)	All leukocytes	Yes	No	ICAM-1, ICAM-2	Adhesion, emigration
CD11b/CD18 (Mac-1, $\alpha_M\beta_2$)	Granulocytes, monocytes	Yes	Yes	ICAM-1	Adhesion, emigration
CD11c/CD18 $\alpha_X\beta_2$	Granulocytes, monocytes	Yes	Yes	fibrinogen, C3b	Activation, adhesion?
$\alpha_4\beta_1$ (VLA-4)	Lymphocytes, monocytes, activated granulocytes	Yes	Yes	VCAM-1, fibronectin	Adhesion
$\alpha_4\beta_7$	Lymphocytes	Yes	No	MadCAM-1, VCAM-1, fibronectin	Rolling, adhesion
$\alpha_E\beta_7$	Lymphocytes, αE is also expressed by dendritic cell subsets	Yes	Yes	E-cadherin	Retention of cells in mucosal sites
Immunoglobulin superfamily					
ICAM-1 (CD54)	Endothelium, monocytes	Yes	Yes	CD11a/CD18, CD11b/CD18	Adhesion, emigration
ICAM-2	Endothelium	Yes	No	CD11a/CD18	Adhesion, emigration
VCAM-1 (CD106)	Endothelium	Yes	Yes	$\alpha_4\beta_1$, $\alpha_4\beta_7$	Adhesion, emigration
MadCAM-1	Endothelium (gut)	Yes	Yes	$\alpha_4\beta_7$, L-selectin	Adhesion, emigration
PECAM-1	Endothelium, leukocytes, platelets	Yes	No	PECAM-1, $\alpha_V\beta_3$?	Adhesion, emigration
VAP-1	Endothelium	Yes	Yes	?	Adhesion

$\alpha_L\beta_2$ (CD11a/CD18; LFA-1), which is primarily expressed by lymphocytes, interacts with intercellular adhesion molecule (ICAM)-1 and ICAM-2.[4] $\alpha_M\beta_2$ (CD11b/CD18) interacts with ICAM-1 on endothelial cells, and is also an important receptor for the complement fragment iC3b. Ligands for $\alpha_X\beta_2$ (CD11c/CD18) include fibrinogen and iC3b; binding of the latter results in cell activation.

A second subfamily of integrins combines the β_1 chain with different α subunits. The $\alpha_4\beta_1$ integrin (VLA-4) is involved in the adhesion of lymphocytes, monocytes, eosinophils, and natural killer cells with cytokine-activated endothelial cells. Ligands for VLA-4 include the vascular cell-adhesion molecule (VCAM)-1, as well as components of the extracellular matrix, such as fibronectin.

The $\alpha_4\beta_7$ heterodimer is highly expressed on a subset of lymphocytes that home towards the gut and gut-associated lymphoid tissues. This heterodimer recognises the mucosal endothelial ligand, mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1), and mediates lymphocyte homing to Peyer's patches.[5] In addition to binding to MAdCAM-1, the $\alpha_4\beta_7$ integrin also binds to VCAM-1 and fibronectin.[6]

As mentioned above, some integrin receptors belong to the immunoglobulin superfamily of

adhesion molecules, which are characterised by the presence of multiple immunoglobulin-like domains. ICAM-1 is constitutively expressed on leukocytes, antigen-presenting cells, fibroblasts, epithelial cells, and endothelial cells. Moreover, it is upregulated upon activation by inflammatory mediators such as tumour necrosis factor alpha (TNF-α).[7,8]

VCAM-1 is an important mediator of lymphocyte and monocyte trafficking, through its interaction with the $\alpha_4\beta_1$ (VLA-4) as well as to $\alpha_4\beta_7$ integrins. Although VCAM-1 is absent on unstimulated human umbilical venule endothelial cells (HUVEC), transcription-dependent upregulation can be elicited by cytokines and lipopolysaccharides (LPS) in these cells.[7] In the murine intestine, the constitutive level of VCAM-1 expression is substantially lower than that of ICAM-1. However, profound increases in the endothelial cell-surface density of VCAM-1 are apparent within 5-9 hours of cytokine stimulation.[7]

The mucosal addressin MAdCAM-1 is mainly expressed on high endothelial venules of Peyer's patches and on venules of the small intestine and colon. MAdCAM-1 serves as a ligand for L-selectin and $\alpha_4\beta_7$ integrin, but not for $\alpha_4\beta_1$, which distinguishes it from VCAM-1. MAdCAM-1 participates in lymphocyte homing to Peyer's patches and in the recruitment of these cells into the intestine during inflammation.[2]

ADHESION MOLECULES IN HUMAN IBD

The contention that vascular endothelial cells are activated in the inflamed intestine of IBD patients is supported by the observation that the capacity of intestinal microvascular endothelial cells isolated from IBD patients to bind leukocytes increases dramatically, relative to those derived from control subjects.[9] It has also been shown that the culture supernatants of colonic mucosal biopsies from patients with UC or CD induce the upregulation of selectins and ICAM-1 in cultured human endothelial cells.[10]

Immunohistochemistry studies of intestinal mucosal biopsies from patients with IBD have demonstrated an increased expression of various endothelial adhesion molecules. In keeping with findings in animal models of IBD, an increased expression of P-selectin and E-selectin in venules and capillaries has been documented in inflamed areas from biopsies and surgically resected specimens in CD and UC.[11-14] Characterisation of ICAM-1 expression in human IBD has produced discrepant results, with initial studies reporting an increased expression of ICAM-1,[12,13] and later studies failing to confirm those findings.[11,14] It has also been observed that the proportion of venular endothelium within the lamina propria that expresses MAdCAM-1 is higher, compared with normal tissues, at inflammatory foci associated with UC and CD.[15] VCAM-1 expression in intestinal mucosa from IBD patients has been reported to be similar to that of controls,[11,12,14] a finding which contrasts with observations in experimental IBD demonstrating a consistent increase in VCAM-1 expression in diverse animal models. This is also at odds with studies involving soluble forms of adhesion molecules, which have shown a marked increase in soluble VCAM-1 in association with active IBD.

INTEGRINS AS TARGETS FOR THERAPEUTIC INTERVENTION

In contrast to members of the immunoglobulin superfamily of adhesion molecules, the function of integrins is regulated by conformational changes in affinity, rather than by changes in their expression levels. Independently of their mechanism of activation, adhesion molecule function can be blocked by means of neutralising monoclonal antibodies, which has proven to be a very effective strategy in limiting both acute and chronic forms of inflammation in animal models.[16-20]

In human IBD, three monoclonal antibodies targeting integrins (natalizumab, vedolizumab and etrolizumab) have been tested in different clinical trials, with the latter two now under development. Tables 2 and 3 summarise clinical trials using anti-adhesion molecule therapies conducted to date in CD and UC, respectively. Natalizumab is a recombinant IgG_4 humanised monoclonal antibody against the α4 integrin and was the first agent generated in the new selective adhesion-molecule inhibitor class. A humanised anti-$\alpha_4\beta_7$ integrin antibody, vedolizumab (MLN-0002), has also progressed to clinical trials in UC and CD. The latter has an IgG1 framework, although Fc-receptor recognition and binding is deleted and this antibody specifically inhibits α4β7 integrin binding with MAdCAM-1. Finally, the anti-β7 integrin antibody rhuMAb β7 has been tested in a Phase I study in UC (NCT00694980).[21]

Table 2. Clinical trials involving drugs targeting adhesion molecules in Crohn's disease.

Study; clinical phase	*Study design*	*Results*	*NCT number; status*
Gordon FH et al.[22] Phase I/II	30 pts with AD received 3 mg/kg infusion of Nat (n=18) or placebo (n=12). PE: CCR (defined as CDAI <150) at wk 2. Pts followed-up until wk 12. PK, tolerability, adverse events and QoL also assessed.	Mean plasma half-life of Nat: 4.8 days, most pts had detectable serum levels of Nat at 4 wks. 39% (7/18) of pts treated receiving Nat achieved complete CR at wk 2, compared to 8% with placebo. The most common adverse events, reported in at least 20% of patients during the 12-wk follow-up period did not significantly differ between the groups.	Completed
Ghosh S et al.[23] Phase II	A randomised, 12-wk study in 248 pts with moderate-to-severe disease in a double-blind, placebo-controlled trial. A four-arm study of Nat consisted of 2 infusions of placebo, 1 infusion of Nat (3 mg/kg) and 1 infusion of placebo, 2 infusions of Nat (3 mg/kg), and 2 infusions of Nat (6 mg/kg). PE: decrease of at least 70 points in CDAI at several time points until wk 12; and for SE: serum CRP and QoL evaluation.	Groups that received 2 infusions of Nat had higher remission rates than the placebo group at multiple time points. Rate of CR was significantly higher in all three Nat groups at wks 4, 6, and 8 than in the placebo group, with highest rate (71%) occurring at 6 wks in the group given 2 infusions of 3 mg/kg. The 2 infusions of 6 mg/kg of Nat and of 3 mg/kg had similar effect. All patients with Nat had a decrease in serum levels of CRP at wk 12, and an improvement in QoL at wk 6. By wk 12, only the groups that received 2 infusions of Nat maintained good QoL compared to the placebo.	Completed
Sandborn WJ et al.[24] ENACT-1 and ENACT-2 studies Phase II/III	Two controlled trials evaluated induction and maintenance therapy in pts with AD. Trial 1: 905 pts randomised to receive 300 mg of Nat or placebo at wks 0, 4, and 8. PE: decrease in CDAI score of at least 70 points, at wk 10. Trial 2: 339 pts randomised to receive 300 mg of Nat or placebo every 4 wks through wk 56. PE: sustained response through wk 36. A secondary outcome in both trials: disease remission (CDAI <150).	Nat and placebo groups had similar rates of response and remission at wk 10 in Trial 1. Higher rates of sustained response (61% vs. 28%) and remission (44% vs. 26%) through wk 36 were verified in the Trial 2. One patient died from progressive multifocal leukoencephalopathy, associated with the JC virus.	NCT00032786 and NCT00032799 Completed

CDAI: Crohn's disease activity index; PK: pharmacokinetics; QoL: Quality of life; CRP: C-reactive protein; wk: week; pts: patients; PE: primary endpoint; AD: active disease; CR: clinical response; Nat: natalizumab; Ved: vedolizumab; Ali: Alicaforsen.

Study; clinical phase	*Study design*	*Results*	*NCT number; status*
Targan SR et al.[25] ENCORE study Phase III	A 12-wk study designed to evaluate Nat efficacy of induction therapy in 509 pts with AD. PE: decrease of >70-point of CDAI at wk 8 sustained through wk 12.	48% of Nat-treated pts and 32% of placebo achieved response at wk 8, sustained through wk 12, with statistical significancy. The frequency and types of adverse events were similar between the groups.	Completed
Feagan BG et al.[36] Phase II	A randomised, double-blind, controlled trial including 185 pts randomised to receive Ved (MLN0002) 2.0 mg/kg, Ved 0.5 mg/kg, or placebo on days 1 and 29. PE: CR (decrease ≥70 points in the CDAI) on day 57. SE: clinical remission (CDAI score <150). PK, tolerability, adverse events and QoL were also assessed.	53% of pts who received Ved 2.0 mg/kg, 49% of those with Ved 0.5 mg/kg and 41% of placebo had CR at day 57. Clinical remission rates were 37%, 30%, and 21%, at day 57. There was 1 infusion-related hypersensitivity reaction.	Completed
Sandborn WJ et al.[37] GEMINI 2 study Phase III	A controlled trial to evaluate induction (wk 6) and maintenance therapy (wk 52) with Ved (300 mg) in pts with AD. 368 pts randomised to Ved or placebo at wks 0 and 2 (cohort 1), and 747 received open-label Ved at wks 0 and 2 (cohort 2). And for maintenance trial, 461 pts were randomised to receive placebo or Ved every 8 or 4 wks until wk 52. Clinical remission (CDAI ≤150) was assessed.	14.5% of the pts in cohort 1 who received Ved and 6.8% who received placebo achieved clinical remission. 39.0% of patients receiving Ved every 8 wks and 36.4% every 4 wks were in clinical remission at wk 52, compared with 21.6% receiving placebo. 24.4% of pts receiving Ved and 15.3% in the placebo group developed serious adverse events, the most common being infections.	NCT00783692 Completed
Yacyshyn B et al.[50] Phase I	331 pts with AD were included in a double-blind placebo-controlled trial to evaluate safety and efficacy (wk 12) of Ali intravenous therapy. PE: clinical remission at wk 12.	There was no difference in clinical remission of Ali-treated pts compared to placebo (33.9% versus 34.5%).	Completed

Table 3. Clinical trials involving drugs targeting adhesion molecules in ulcerative colitis.

Study; clinical phase	Study design	Results	NCT number; status
Gordon FH et al.[26] Phase I	A pilot study of 10 pts with AD, who received a single 3 mg/kg infusion of Nat. PE: decrease of Powell-Tuck score at 2 wks post-infusion. CRP, adverse events and QoL were also assessed.	5 pts achieved a CR at wk 2 and 1 more pt at wk 4, defined by Powell-Tuck score ≤5. 1 patient did not complete follow-up due to severe disease requiring urgent colectomy.	Completed
Feagan BG et al.[39] Phase II	A double-blind, placebo-controlled trial of Ved (MLN 02) therapy in AD designed to evaluate dose-response. 181 pts received Ved at 0.5 mg/kg or 2.0 mg/kg or placebo on day 1 and day 29. Clinical remission (a decreased of at least 3 points in the ulcerative colitis clinical score, a modification of the scoring system of the Mayo Clinic, MCS) and endoscopic remission (modified Baron score=0) was assessed at wk 6.	33% of pts who received Ved at 0.5 mg/kg, 32% of those with Ved at 2.0 mg/kg and 14% of placebo were in clinical remission at wk 6. 28% of pts who received Ved 0.5 mg/kg, 12% of those with Ved 2.0 mg/kg and 8% of placebo had endoscopic remission at wk 6.	Completed
Feagan BG et al.[38] GEMINI 1 study Phase II	A controlled trial to evaluate induction (wk 6) and maintenance therapy (wk 52) with Ved (300 mg) in pts with AD. 374 pts were randomised to receive Ved or placebo at wks 0 and 2 (cohort 1), and 521 received open-label Ved at wks 0 and 2 (cohort 2). For maintenance trial, 461 pts were randomised to receive placebo or Ved every 8 or 4 wks until wk 52. Clinical remission (decrease of 3 points in MCS and a decrease of at least 30% from baseline) was assessed.	47.1% of the pts in cohort 1 who received Ved and 25.5% who received placebo achieved clinical remission. 41.8% of pts receiving Ved every 8 wks and 44.8% every 4 wks were in clinical remission at wk 52, compared with 15.9% with placebo.	NCT00783718 Completed
Rutgeerts PJ et al.[21] Phase I	A double-blind, placebo-controlled trial of Etr therapy in moderate-to-severe disease designed to evaluate safety, PK and dose-response at day 29, 43, and 71. 49 pts participated on the study.	12/18 pts had clinical remission, compared with 4/5 placebo. 3/18 pts had clinical remission in the multiple dose stage, while 1/5 in placebo. Headache was the most common adverse event.	NCT00694980 Completed
Vermeire S et al.[45] Phase II	A double-blind, placebo-controlled study including 124 pts with AD that were randomised to Etr 100 mg monthly SC or 300 mg monthly SC + loading dose of 420 mg SC between wk 0 and 2 or placebo for 3 doses. PE: clinical remission at wk 10, defined as a total MCS of ≤2. SE: endoscopic remission (endoscopic score=0).	20.5% of pts treated with Etr 100 mg, 10.3% of those with 300 mg and 0% of placebo achieved clinical remission at week 10. In the anti-TNF-α naïve subgroup, the rates of clinical remission were significantly higher in the 100 mg dose group compared with placebo (43.8% versus 0%). 10.3% of pt treated with Etr 100 mg, 7.7% of those with 300 mg and 0% of placebo achieved endoscopic remission. In the anti-TNF-α naïve subgroup, endoscopic remission was 25% and 16.7% vs. 0% respectively.	Completed

DAI: disease activity index; MCS: Mayo Clinic Score; PK: pharmacokinetics; QoL: Quality of life; CRP: C-reactive protein; wk: week; pts: patients; PE: primary endpoint; AD: active disease; CR: clinical response; Nat: natalizumab; Ved: vedolizumab; Ali: Alicaforsen; Etr: etrolizumab; Mes: mesalazine.

Study; clinical phase	Study design	Results	NCT number; status
van Deventer SJ et al.[51] Phase I	40 pts with AD were included in a randomised, double-blind, placebo-controlled trial to evaluate safety and efficacy of Ali enema therapy. PE: assessment of DAI in several time points until month 6. Mean % change in DAI for each treatment group was evaluated at each time point and compared to placebo.	Ali at 2 and 4 mg/ml improved DAI by 72% and 68% compared with a placebo response of 11.5% at month 3. There were no significant differences between groups at month 6.	Completed
van Deventer SJ et al.[52] Phase II	A randomised, placebo-controlled, double-blind trial to evaluate efficacy and dose response (120 mg, 240 mg in 5 treatment arms) of Ali enema therapy in 112 pts with active distal disease and/or mild-to-moderate left-sided disease. PE: mean % change of DAI from wk 0 to 6. Mean % change in DAI for each treatment group was evaluated at each time point and compared to placebo.	No difference in DAI of Ali-treated pts compared to placebo (33.9% versus 34.5%). A reduction in mean % change of DAI relative to baseline was observed in the daily 240 mg Ali enema arm compared to placebo from wk 18 to 30.	Completed
Miner Jr PB et al.[53] Phase II	A randomised, double-blind, controlled trial with 159 pts with AD, to evaluate safety and efficacy of Ali enema (120 mg, 240 mg) compared to Mes enema (4 g). PE: DAI at wk 6 following either Ali enema or Mes enema therapy. DAI also assessed at different time points up to wk 54.	No significant difference in CR at wk 6 observed between treatment arms. Duration of response to Ali enema was 2 to 3-fold longer (128 and 146 days) compared to Mes (54 days).	Completed
Vermeire S et al.[54] Phase I/II	A randomised, double-blind, placebo-controlled study to evaluate safety and efficacy (remission based on Mayo score and on levels of faecal calproctectin) at wk 4 and 12. 80 pts with AD received single or multiple (3 doses, 4-wk intervals) doses of PF-00547,659 0.03-10 mg/kg IV/SC, or placebo. Endoscopic response assessed by ≥3-point reduction and 30% improvement in total Mayo score, and ≥1-point decrease in rectal bleeding subscore or absolute rectal bleeding score of 0 or 1. Remission rates were defined as the proportion of patients with a total Mayo score ≤2 points with no individual subscore exceeding 1 point.	Rates of remission with PF-00547,659 were 13% at wk 4 and 22% at wk 12; and 11% at wk 4 and 0% at wk 12 for placebo group. Rates of endoscopic response were 42% in the PF-00547,659 group and 29% in the placebo group.	NCT00928681 Completed

Natalizumab

Several placebo-controlled studies involving hundreds of recruited patients have demonstrated the efficacy of natalizumab in achieving clinical remission in CD patients.[22-24] Nonetheless, Phase II and Phase III natalizumab trials failed to show statistically significant differences at the predefined endpoint. An additional Phase III induction study (ENCORE; Efficacy of Natalizumab in Crohn's Disease Response and Remission) involving 509 CD patients was conducted. This study achieved its primary efficacy endpoint: induction of response, defined as >70-point decrease from baseline in CDAI at week 8 sustained through week 12. Sustained remission occurred in 26% of natalizumab-treated patients and in 16% of patients receiving placebo ($p<0.002$).[25] The most promising results, however, were seen in the maintenance phase (ENACT-2).[24] 61% of CD patients receiving natalizumab maintained their response for an additional 6 months compared with 28% in the placebo group ($p<0.001$), and this significant difference was maintained for an additional 12 months.

This might be related to the drug's mechanism of action. If natailzumab exerts its beneficial effect predominantly by blocking leukocyte recruitment to sites of inflammation, once the inflammatory process is ongoing the infiltrating lymphocytes have a high resistance to apoptosis and may remain in the intestine, thereby perpetuating inflammation for considerable periods, and thus requiring administration of natalizumab for a prolonged period (10-12 weeks) in order to achieve a significant effect. On the other hand, once the inflammatory cells have been eliminated, prevention of further recruitment is very effective in countering a new relapse.

Data evaluating the efficacy of natalizumab treatment in UC are scarce. The only full publication available involves a pilot uncontrolled study, in which 10 patients with active UC, defined as a Powell-Tuck score >4, received a single infusion of natalizumab (3 mg/kg). The median Powell-Tuck score significantly decreased from 10.0 at baseline to 7.5 at week 2 and then to 6.0 at week 4. Five of the 10 patients achieved a clinical response, defined as a Powell-Tuck score of ≤5 by week 2, and one additional patient responded by week 4. Two patients achieved complete remission, defined as a score of 0. The median CRP at 2 weeks was also decreased.[26] Despite the positive efficacy demonstrated in this study, further investigation of natalizumab in UC is unlikely in the future due to life-threatening safety issues with the drug (see below) and the fact that surgery is a widely accepted option for UC patients refractory to current available therapies.

Safety of Natalizumab

The major setback in the clinical application of natalizumab has been reports of three serious infectious adverse events: onset of PML, which occurred in two patients (one fatal) treated in clinical trials for multiple sclerosis,[27,28] and one case (fatal) of a CD patient 3 months after initiation of open-label natalizumab treatment upon completion of participation in the ENACT-2 trial.[29] PML is a rare opportunistic infection of the central nervous system caused by the JC (John Cunningham, the first patient in whom the disease was recognised) virus.[30] PML is usually irreversible and fatal.

These three cases of PML in patients treated with natalizumab led the Food and Drug Administration (FDA) to withdraw the drug from the market in 2005. Following a safety evaluation, in >3,500 patients with multiple sclerosis (MS) or CD, that found no new cases of PML,[31] natalizumab was reintroduced to the market in 2006. Natalizumab is currently approved as a monotherapy for severe relapsing-remitting MS refractory to all other treatments, and for CD after failure of anti-TNF agents. Centres where natalizumab may be used are limited, and patients treated with the drug must participate in an extensive safety monitoring programme.[32] A recent report on this programme revealed that, of 37,600 patients being treated with this drug in the 3 years since the reintroduction of natalizumab to the market, there have been five additional cases of PML in patients with MS.[33] It is interesting to note that three recently reported cases of PML occurred in psoriasis patients treated with efalizumab, an antibody directed against the integrin αL (CD11a).[34]

Vedolizumab

Since natalizumab is an anti-α_4 antibody, it blocks both $\alpha_4\beta_7$ and $\alpha_4\beta_1$ integrins, and consequently all VCAM-1 and MAdCAM-1 mediated leukocyte-endothelial cell interactions. It is conceivable that a more selective blockade may bring about

a more favourable safety profile; e.g. a blockade of $\alpha_4\beta_7$-MAdCAM-1 interactions, given the highly predominant expression of MAdCAM-1 in the gastrointestinal tract and the complete absence of expression of this molecule in the brain vasculature.[35] Vedolizumab (MLN-0002) is a blocking antibody against the $\alpha_4\beta_7$ integrin, and its efficacy for treatment of CD[36] and UC has been tested in Phase II studies, which have been followed by ongoing Phase III trials.[37,38]

The efficacy of vedolizumab for induction of remission in UC was assessed in a Phase II multicentre, double-blind, placebo-controlled trial in which 181 patients were assigned to receive vedolizumab (0.5 or 2.0 mg/kg) or placebo intravenously on days 1 and 29.[39] Clinical remission rates at week 6 were 33%, 32%, and 14%, respectively (p=0.03). The corresponding proportions of patients who improved by at least 3 points on the UC clinical score were 66%, 53%, and 33% (p=0.002). 28% of patients receiving 0.5 mg/kg and 12% of those receiving 2.0 mg/kg had endoscopically evident remission, compared with 8% of those receiving placebo (p=0.007). Human anti-human antibodies developed in 44% of those patients who received vedolizumab. High titres of anti-drug antibodies were present in 24% of patients and were associated with incomplete saturation of the $\alpha_4\beta_7$ receptor on circulating lymphocytes and no clinical benefits from treatment. No important differences in the occurrence of adverse events were identified among the treatment groups. No deaths, cancers, or opportunistic infections were observed.

The results of two integrated randomised, double-blind, placebo-controlled trials in UC have recently been published.[37,38] These studies evaluated the effect of vedolizumab (300 mg intravenously [i.v.]) at weeks 0 and 2 as induction (at week 6) and maintenance therapy (up to 52 weeks). A clinical response (decrease in the Mayo score of at least 3 points and no less than 30% from baseline with at least a 1-point reduction in the rectal bleeding subscore) was seen in 47.1% of vedolizumab-treated patients compared to 25.5% of placebo patients (p<0.001). At week 52, >40% of patients receiving vedolizumab every 4 or 8 weeks were in clinical remission (Mayo score ≤2 and no subscore >1), compared with 15.9% of patients who switched to placebo (p<0.001).

A significant benefit of vedolizumab was also reported for CD patients, although the results were less dramatic, and the frequency of adverse events higher than in UC.

rhuMAb β7 (Etrolizumab)

rhuMAb β_7 is a humanised IgG1 monoclonal antibody that targets the β_7 integrin subunit. Thus, while it may provide similar potential therapeutic benefits to vedolizumab by blocking $\alpha_4\beta_7$-dependent leukocyte recruitment and cell activation, it also recognises another β_7 integrin, $\alpha_E\beta_7$, which plays other roles in gut-associated immune responses. $\alpha_E\beta_7$ is expressed by most intra-epithelial lymphocytes (IELs) and binds to the epithelial E-cadherin expressed by the epithelium. It can also be expressed by some lamina propria lymphocytes (LPLs) with regulatory properties,[40] as well as a subset of tolerogenic dendritic cells resident in the intestine or associated lymphoid tissues.[41,42] Nonetheless, the functional role of α_E expression in these cell populations is not clear and, at least in α_E-deficient mice, expression of $\alpha_E\beta_7$ T cells is not needed to drive their accumulation in the intestine,[43] nor is it necessary for mesenteric lymph node dendritic cells to induce gut-tropic ($\alpha_4\beta_7$ and CCR9) receptors on T cells.[44]

A recently published randomised Phase I study evaluated the safety and pharmacology of rhuMAb β_7 in UC.[21] This study showed that while rhuMAb β_7 is safe in UC patients, it offers no significant benefits compared to the placebo, at least not in this small series of patients. Nonetheless, results from a Phase II study in UC patients show much more promise with etrolizumab (100 mg or 300 mg), demonstrating significantly higher rates of clinical remission compared to placebo at week 10, as well as increased endoscopic remission. The differences compared to placebo were even more pronounced in patients naïve to anti-TNF-α.[45]

IMMUNOGLOBULIN SUPERFAMILY ADHESION MOLECULES AS TARGETS FOR THERAPEUTIC INTERVENTION IN UC

Anti-ICAM-1

An antisense phosphorothioate oligodeoxynucleotide (ODN) to mouse ICAM

1, ISIS 3082, has been shown to be active in multiple models of inflammation, including dextran sulphate-induced colitis.[46] The human analogue alicaforsen (ISIS 2302)[47] has been tested in a pilot study in CD where it showed some benefits.[48] However, a blinded controlled study involving fixed doses of subcutaneous ISIS 2302 did not show higher effectiveness than the placebo.[49] The global results of two blinded controlled studies including a total of 331 patients with active CD also showed that the remission rates in the ISIS 2302-treated and placebo groups were similar.[50]

An enema formulation of ISIS-2302 for treatment of UC was tested in a small, randomised, placebo-controlled, double-blind, dose-escalating trial with encouraging results.[51] However, this study was followed by two larger and negative studies.[52,53] Further development of this drug in IBD is highly unlikely.

Anti-MAdCAM-1

Blocking MAdCAM-1 is a rational mechanism of action for therapeutic intervention in IBD, since its expression is mainly restricted to the gastrointestinal tract mucosa.[54] This organ specificity may translate to a favourable safety profile.

A recent Phase I study tested the safety and efficacy of a fully human anti-MAdCAM-1 IgG2 antibody (PF-00547,659) in patients with active UC.[54] In this double-blind, placebo-controlled study, 80 patients with active UC received a single dose or three doses at 4-week intervals of PF-00547,659 (0.03–10 mg/kg IV/SC) or placebo. No obvious side-effects were observed in the monoclonal antibody-treated patients, compared to placebo; importantly, there was no evidence of opportunistic infections. The active treatment arm had numerically higher response rates and remission rates at weeks 4 and 12, although none of these comparisons reached statistical significance.

Overall responder/remission rates at weeks 4 and 12 were 52%/13% and 42%/22%, respectively, for PF-00547,659 and 32%/11% and 21%/0%, respectively, for placebo. Faecal calprotectin levels decreased to a greater extent with PF-00547,659 than placebo (week 4: 63% versus 18%). In this study, no antidrug antibodies were detected during treatment up to week 12 for all patients, and no injection site reactions were observed. Longer-term studies involving a much larger number of patients are required and are now underway.

CONCLUSIONS

Several key steps in the inflammatory cascade that result in leukocyte recruitment appear amenable to pharmacological inhibition and represent an attractive target for the treatment of IBD, including UC. Although preliminary use in clinical practice has been encouraging, the challenges posed by the potential for disruption of alternate physiological processes, as well as immune suppression, remain significant. Given its intestinal mucosal restricted expression, modulation of the $\alpha_4\beta_7$-MAdCAM-1 interaction seems at present the more promising approach. The development of safe and effective drugs that target these molecular components of the inflammatory response may yield novel and improved therapies for UC patients.

REFERENCES

1. Perrier C, Rutgeerts P. New drug therapies on the horizon for IBD. Dig Dis. 2012;30 Suppl 1:100-5.

2. Panés J, Granger DN. Leukocyte-endothelial cell interactions: molecular mechanisms and implications in gastrointestinal disease. Gastroenterology. 1998;114:1066-90.

3. Luo BH et al. Structural basis of integrin regulation and signaling. Annu Rev Immunol. 2007;25:619-47.

4. Panés J et al. Leukocyte-endothelial cell adhesion: avenues for therapeutic intervention. Br J Pharmacol. 1999;129:1-14.

5. Tsuzuki Y et al. alpha 4 integrin plays a critical role in early stages of T lymphocyte migration in Peyer's patches of rats. Intl Immunol. 1996;8:287-95.

6. Berlin C et al. alpha 4 integrins mediate lymphocyte attachment and rolling under physiologic flow. Cell. 1995;80:413-22.

7. Henninger DD et al. Cytokine-induced VCAM-1 and ICAM-1 expression in different organs of the mouse. J Immunol. 1997;158:1825-32.

8. Panés J et al. Regional differences in constitutive and induced ICAM-1 expression in vivo. Am J Physiol. 1995;269:H1955-64.

9. Binion DG et al. Enhanced leukocyte binding by intestinal microvascular endothelial cells in inflammatory bowel disease. Gastroenterology. 1997;112:1895-907.

10. Pooley N et al. Up-regulation of E-selectin and intercellular adhesion molecule-1 differs between Crohn's disease and ulcerative colitis. Dig Dis Sci. 1995;40:219-25.

11. Cellier C et al. In-situ endothelial cell adhesion molecule expression in ulcerative colitis. E-selectin in-situ expression correlates with clinical, endoscopic and histological activity and outcome. Eur J Gastroenterol Hepatol. 1997;9:1197-203.

12. Koizumi M et al. Expression of vascular adhesion molecules in inflammatory bowel disease. Gastroenterology. 1992;103:840-7.

13. Nakamura S et al. In situ expression of the cell adhesion molecules in inflammatory bowel disease. Evidence of immunologic activation of vascular endothelial cells. Lab Invest. 1993;69:77-85.

14. Oshitani N et al. Adhesion molecule expression on vascular endothelium and nitroblue tetrazolium reducing activity in human colonic mucosa. Scand J Gastroenterol. 1995;30:915-20.

15. Briskin M et al. Human mucosal addressin cell adhesion molecule-1 is preferentially expressed in intestinal tract and associated lymphoid tissue. Am J Pathol. 1997;151:97-110.

16. Hesterberg PE et al. Rapid resolution of chronic colitis in the cotton-top tamarin with an antibody to a gut-homing integrin alpha 4 beta 7. Gastroenterology. 1996;111:1373-80.

17. Podolsky DK et al. Attenuation of colitis in the cotton-top tamarin by anti-alpha 4 integrin monoclonal antibody. J Clin Invest. 1993;92:372-80.

18. Picarella D et al. Monoclonal antibodies specific for beta 7 integrin and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) reduce inflammation in the colon of scid mice reconstituted with CD45RBhigh CD4+ T cells. J Immunol. 1997;158:2099-106.

19. Sans M et al. VCAM-1 and ICAM-1 mediate leukocyte-endothelial cell adhesion in rat experimental colitis. Gastroenterology. 1999;116:874-83.

20. Soriano A et al. VCAM-1, but not ICAM-1 or MAdCAM-1, immunoblockade ameliorates DSS-induced colitis in mice. Lab Invest. 2000;80:1541-51.

21. Rutgeerts PJ et al. A randomised phase I study of etrolizumab (rhuMAb beta7) in moderate to severe ulcerative colitis. Gut. 2013;62:1122-30.

22. Gordon FH et al. A randomized placebo-controlled trial of a humanized monoclonal antibody to alpha4 Integrin in active Crohn's disease. Gastroenterology. 2001;121:268-74.

23. Ghosh S et al. Natalizumab for active Crohn's disease. N Engl J Med. 2003;348:24-32.

24. Sandborn WJ et al. Natalizumab induction and maintenance therapy for Crohn's disease. N Engl J Med. 2005;353:1912-25.

25. Targan SR et al. Natalizumab for the treatment of active Crohn's disease: results of the ENCORE Trial. Gastroenterology. 2007;132:1672-83.

26. Gordon FH et al. A pilot study of treatment of active ulcerative colitis with natalizumab, a humanized monoclonal antibody to alpha-4 integrin. Aliment Pharmacol Ther. 2002;16:699-705.

27. Kleinschmidt-DeMasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. N Engl J Med. 2005;353:369-74.

28. Langer-Gould A et al. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. N Engl J Med. 2005;353:375-81.

29. Van Assche G et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. N Engl J Med. 2005;353:362-8.

30. Padgett BL et al. Cultivation of papova-like virus from human brain with progressive multifocal leucoencephalopathy. Lancet. 1971;297:1257-60.

31. Yousry TA et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. N Engl J Med. 2006;354:924-33.

32. Greenlee JE. Progressive multifocal leucoencephalopathy in the era of natalizumab: a review and discussion of the implications. Int MS J. 2006;13:100-7.

33. Carson KR et al. Monoclonal antibody-associated progressive multifocal leucoencephalopathy in patients treated with rituximab, natalizumab, and efalizumab: a Review from the Research on Adverse Drug Events and Reports (RADAR) Project. Lancet Oncol. 2009;10:816-24.

34. Ladizinski B et al. Progressive multifocal leukoencephalopathy and reversible progressive leukoencephalopathy syndrome in dermatologic therapy. J Drugs Dermatol. 2013;12:e20-4.

35. Pullen N et al. Mucosal addressing cell adhesion molecule (MAdCAM) is not expressed in normal and MS brain. Gastroenterology. 2009;136 Suppl 1:A678.

36. Feagan BG et al. Treatment of active Crohn's disease with MLN0002, a humanized antibody to the alpha4beta7 integrin. Clin Gastroenterol Hepatol. 2008;6:1370-7.

37. Sandborn WJ et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013;369:711-21.

38. Feagan BG et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369:699-710.

39. Feagan BG et al. Treatment of ulcerative colitis with a humanized antibody to the alpha4beta7 integrin. N Eng J Med. 2005;352:2499-507.

40. Uss E et al. CD103 is a marker for alloantigen-induced regulatory CD8+ T cells. J Immunol. 2006;177:2775-83.

41. Iliev ID et al. The yin and yang of intestinal epithelial cells in controlling dendritic cell function. J Exp Med. 2007;204:2253-7.

42. Schlickum S et al. Integrin alpha E(CD103)beta 7 influences cellular shape and motility in a ligand-dependent fashion. Blood. 2008;112:619-25.

43. Lefrancois L et al. The role of beta7 integrins in CD8 T cell trafficking during an antiviral immune response. J Exp Med. 1999;189:1631-8.

44. Jaensson E et al. Small intestinal CD103+ dendritic cells display unique functional properties that are conserved between mice and humans. J Exp Med. 2008;205:2139-49.

45. Vermeire S et al. Differentiation between Etrolizumab (Rhumab beta7) and placebo in the Eucalyptus phase II randomized double-blind placebo-controlled induction study to evaluate efficacy and safety in patients with refractory moderate-to- severely active ulcerative colitis. Gastroenterology. 2012;S36:157.

46. Bennett CF et al. An ICAM-1 antisense oligonucleotide prevents and reverses dextran sulfate sodium-induced colitis in mice. J Pharmacol Exp Ther. 1997;280:988-1000.

47. Crooke ST. Progress in antisense technology. Annu Rev Med. 2004;55:61-95.

48. Yacyshyn BR et al. A placebo-controlled trial of ICAM-1 antisense oligonucleotide in the treatment of Crohn's disease. Gastroenterology. 1998;114:1133-42.

49. Schreiber S et al. Absence of efficacy of subcutaneous antisense ICAM-1 treatment of chronic active Crohn's disease. Gastroenterology. 2001;120:1339-46.

50. Yacyshyn B et al. A randomized, double-masked, placebo-controlled study of alicaforsen, an antisense inhibitor of intercellular adhesion molecule 1, for the treatment of subjects with active Crohn's disease. Clin Gastroenterol Hepatol. 2007;5:215-220.

51. van Deventer SJ et al. A randomised, controlled, double blind, escalating dose study of alicaforsen enema in active ulcerative colitis. Gut. 2004;53:1646-51.

52. van Deventer SJ et al. A phase II dose ranging, double-blind, placebo-controlled study of alicaforsen enema in subjects with acute exacerbation of mild to moderate left-sided ulcerative colitis. Aliment Pharmacol Ther. 2006;23:1415-25.

53. Miner PB Jr. et al. Safety and efficacy of two dose formulations of alicaforsen enema compared with mesalazine enema for treatment of mild to moderate left-sided ulcerative colitis: a randomized, double-blind, active-controlled trial. Aliment Pharmacol Ther. 2006;23:1403-13.

54. Vermeire S et al. The mucosal addressin cell adhesion molecule antibody PF-00547,659 in ulcerative colitis: a randomised study. Gut. 2011;60:1068-75.

EFFECTS OF ANTIBIOTIC USE ON THE MICROBIOTA OF THE GUT AND ASSOCIATED ALTERATIONS OF IMMUNITY AND METABOLISM

M. Pilar Francino,[1,2] Andrés Moya[1,3]

1. Senior Scientist, Joint Research Unit for Genomics and Health, Foundation for the Promotion of Health and Biomedical Research in Valencia (FISABIO-Public Health), Cavanilles Institute of Biodiversity and Evolutionary Biology, University of Valencia, Valencia, Spain
2. Adjunct Assistant Professor, School of Natural Sciences, University of California Merced, CA, USA
3. Senior Scientist, Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), Spain

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ABSTRACT

The excessively widespread use of antibiotics has created many threats. A well-known problem is the increasing bacterial resistance to antibiotics, which has clearly become a worldwide challenge to the effective control of infections by many pathogens. But, beyond affecting the pathogenic agents for which it is intended, antibiotic treatment also affects the mutualistic communities of microbes that inhabit the human body. As they inhibit susceptible organisms and select for resistant ones, antibiotics can have strong immediate effects on the composition of these communities, such as the proliferation of resistant opportunists that can cause accute disease. Furthermore, antibiotic-induced microbiota alterations are also likely to have more insidious effects on long-term health. In the case of the gut microbiota, this community interacts with many crucial aspects of human biology, including the regulation of immune and metabolic homeostasis, in the gut and beyond. It follows that antibiotic treatments bear the risk of altering these basic equilibria. Here, we review the growing literature on the effects of antibiotic use on gut microbiota composition and function, and their consequences for immunity, metabolism, and health.

Keywords: Antibiotics, human microbiome, gut microbiota, pathogenic bacteria, infection, immunity, autoimmunity, immunotolerance, atopy, inflammation, metabolism, obesity, metabolic syndrome.

INTRODUCTION

The gut harbours the most dense and complex microbiota of the human body, which contributes importantly to several basic physiological functions, including nutrition, defence against pathogens, and metabolic and immune homeostasis. Consequently, disturbances in the composition and function of the gut microbiota, i.e. dysbioses, can have severe consequences for health at several different levels.[1,2] In particular, evidence is mounting for the involvement of dysbioses in the broad variety of health problems associated to immune and metabolic malfunctions. Antibiotics are one of the main factors causing dysbiosis and therefore play a significant role in generating the associated suite of undesirable health effects. In this review, we will first address the direct effects of antibiotics on the gut microbiota, and we will then discuss how antibiotic-induced dysbioses relate to immune and metabolic health, and the underlying mechanisms likely to be responsible for such relationships.

EFFECTS OF ANTIBIOTICS ON THE GUT MICROBIOTA

Numerous works employing different technologies have explored the effects of antibiotics on the

composition of the gut microbiota. These studies have been consistent in demonstrating that dysbiosis can ensue upon antibiotic administration. In the case of broad-spectrum antibiotics, deep 16S rRNA gene pyrosequencing showed that the abundances of roughly one-third of the bacterial taxa in the gut microbiota could be affected, decreasing the taxonomic richness, diversity, and evenness of the community.[3] Moreover, the effect of antibiotic administration on gut microbiota composition is rapid, as drastic losses of diversity and abundance shifts can occur within 3 days of drug initiation.[4] After termination of antibiotic treatment, the gut microbiota presents a certain degree of resilience, in that it is usually capable of returning to a composition more similar to the one it had before. However, a complete return to the initial state is often not achieved. Several studies have followed-up the progress of gut microbiota composition during months to years after treatment, demonstrating that differences can remain after long periods of time.[3-6] Mouse models have similarly revealed long-lasting gut microbiota alterations induced by different antibiotics, including ampicillin, cefoperazone or vancomycin.[7,8]

More recently, the characterisation of the effects of antibiotics on the gut microbiota has been extended to multi-omic analyses, demonstrating that antibiotic treatment not only alters the taxonomic composition, but also the overall gene expression, protein activity and metabolism of the community. Monitoring of the gut microbiota during and after 14-days of β-lactam therapy revealed that the metabolome was maximally altered by day 6 after the initiation of treatment, whereas maximum change in taxonomic composition was not reached until day 11, when richness and diversity were lowest.[9] This shows that the gut microbiota can modify its metabolic activity in response to antibiotic stress much faster than the relative survival and growth of different bacterial taxa, which will affect community structure. Further to this, the carbohydrate-degrading enzymatic activities of the total gut microbiota from β-lactam-treated patients were experimentally measured, showing that these subjects had high and unbalanced sugar anabolic capacities, similar to those observed in obese individuals.[10] In a different approach, the short-term alteration of microbial physiological state and activity was analysed after *ex vivo* incubation of faecal samples with different antibiotics.[11] In most cases, antibiotic exposure increased the proportion of gut microbiota cells with damaged membranes, particularly for cell wall synthesis inhibitors, such as ampicillin and vancomycin. These antibiotics also affected which fractions of the gut microbiota were more or less active, as judged by the amount of nucleic acids detected within the cell. In particular, after ampicillin treatment the proportion of Bacteroidetes increased within the most active gut microbiota fraction. Antibiotics also affected community-wide gene expression, with increases in the expression of genes for antibiotic resistance, stress response, and phage induction. In addition, those antibiotics that act by inhibiting translation, such as tetracycline and the macrolides, also resulted in an increased expression of genes related to genetic information processing (e.g. transcription and translation). Overall, these works clearly demonstrate that antibiotics alter not only the taxonomic composition, but also the functioning of the gut microbiota, and therefore stress their potential to impact on the numerous human physiology processes that rely on microbial activities.

ANTIBIOTIC-INDUCED GUT MICROBIOTA

Alterations on the Immune System and Related Health Problems

The impact of antibiotics on the gut microbiota has short and long-term effects on the development and operation of the immune system that can generate a variety of health problems. Such problems relate mainly to a decreased resistance to infection or to a disrupted immune homeostasis, which may result in atopic, inflammatory or autoimmune disease.

Decreased Resistance to Infection

In the short-term, drastic alterations of gut microbiota composition and function can affect the immediate risk for intestinal infection due to the acquisition and spread of incoming pathogens or to the opportunistic pathogenic behaviour of some resident members of the gut microbiota. An important example of this problem is the prevalence of antibiotic-associated diarrhoea (AAD), caused by intestinal overgrowth of common nosocomial pathogens such as *Klebsiella pneumoniae*, *Staphylococcus aureus* and, most frequently, *Clostridium difficile* (*C. difficile*).[12-15]

Importantly, *C. difficile* can cause a varying degree of ailments from a single, self-limiting episode of diarrhoea to more intractable, long-term problems with recurrent infections.[1,16] The gut microbiota of patients infected with *C. difficile* has decreased diversity,[17] and a mouse model has shown that treatment with clindamycin produces long-lasting changes in the small and large intestinal microbiota, with loss of approximately 90% of the cecal taxa, which can be followed by a state of chronic *C. difficile* infection.[18,19] It has been postulated that AAD may also result from *Candida* overgrowth,[20-22] although elevated numbers of intestinal *Candida* can be a consequence of antibiotic treatment or diarrhoea per se rather than a direct cause of AAD.[23]

The effects of antibiotics on the capacity of the immune system to battle infection probably proceed through several related ways, involving both innate and adaptive immunity. Antibiotic-induced gut microbiota changes can alter the type and diversity of microbial-associated molecular patterns (MAMPS) that are encountered by receptors such as the cytosolic NOD1 and the membrane-spanning Toll-like receptors (TLRs), present in various intestinal epithelial cells (IECs) and innate immunity cells. In turn, the altered stimulation of these receptors can impact numerous processes, from the development of intestinal lymphoid tissues to the differentiation of T cell subtypes, the priming of neutrophils for bacterial killing, the production of antibacterial molecules, and the release of cytokines and pro-cytokines with a variety of functions.[24] For instance, treatment of mice with metronidazole, neomycin and vancomycin diminishes expression of Reg3γ, a lectin with bactericidal activity against Gram-positives, the expression of which is normally induced through the interaction of MAMPS with TLRs present in the surface of T cells and IECs; as a result, vancomycin-resistant *Enterococcus* (VRE) colonisation of the small and large intestine is facilitated, potentially leading to a state where >97% of the gut microbiota is VRE.[8,25,26] Similarly, administration of a cocktail of antibiotics containing ampicillin, neomycin, metronidazole, and vancomycin depletes the gut microbiota and diminishes the level of the MAMP peptidoglycan, which reduces the neutrophil-mediated killing of *Streptococcus pneumoniae*.[27] Also, immune responses against viral infection can be affected by the antibiotic-induced alteration of pro-cytokine expression; for example, neomycin, an antibiotic that predominantly kills Gram-negative bacteria, decreases the expression of the pro-interleukins (IL) pro-IL-1β and pro-IL-18, impairing responses against the influenza virus.[28] Regarding adaptive immunity, amoxicillin-induced gut microbiota changes have been shown to reduce expression of Major Histocompatibility Complex (MHC) Class I and Class II genes in the small and large intestine, as well as serum levels of immunoglobulin G (IgG).[29]

Disrupted Immune Homeostasis and Tolerance

Beyond increasing the risk for infection, antibiotic-induced alterations of the gut microbiota can affect basic immune homeostasis with body-wide and long-term repercussions. Atopic, inflammatory, and autoimmune diseases have been linked to gut microbiota dysbiosis. For example, a metagenomic approach applied to Crohn´s disease (CD) patients highlighted a reduction in Firmicutes (particularly *Clostridium leptum*) and an increase of some Gram-negative bacteria (Porphyromonadaceae) often responsible for inflammatory processes.[30,31] In the case of irritable bowel syndrome (IBS), which is the most common functional gastrointestinal disorder in Western countries, alterations in the gut microbiota have also been detected,[32-34] accompanied by an over-secretion of microbial organic acids.[35] Although no consensus has been reached regarding the association between specific bacteria and IBS, the gut microbiota of IBS patients has a reduced diversity. Moreover, IBS often follows bouts of gastrointestinal infection (post-infectious IBS) and there is evidence to suggest that antibiotics may play a role in the pathogenesis of the disorder.[36]

The effects of dysbiosis will be ever more relevant if they occur early in life, when the immune system is maturing and immunological tolerance is being established. For instance, CD has been shown to increase in children treated with antibiotics during their first 5 years.[37] Also, it has been known for decades that the specific composition of the gut microbiota during infancy and early childhood is linked to the relative occurrence of atopic diseases.[38-40] In this respect, a protective role against atopy has often been reported for lactic acid bacteria (LAB), mainly *Bifidobacteria* and *Lactobacillus*,[41-43] whereas high abundances of *Escherichia coli* and other enterics have been linked to eczema and other

allergies.[40,44-46] Furthermore, some relationships between gut microbiota composition and atopic disease, such as the association between eczema and a low-diversity microbial community dominated by enterobacteria, may extend back to the intrauterine stage, since this type of microbiota is more prevalent in the meconium of newborns who later on will develop this disease, and in those whose mothers are affected by it.[47] However, the link between allergies and antibiotic use during early life has yet to be firmly established, as associations have been found in some epidemiological studies but not in others.[48-50]

At the cellular and molecular level, the mechanisms by which gut microbiota species interact with components of the immune system to impact the development of immunotolerance are currently debated.[39,51-54] Until recently, the most critical factor in maintaining immune homeostasis was thought to be the balance between the adaptive immunity Th1 and Th2 helper cell subsets. Indeed, excessive Th1 or Th2 activation results in chronic inflammatory and autoimmune disease or in allergic disease, respectively.[55,56] However, new lines of evidence indicate that other factors are important for immune balance, including a major role for regulatory T cells (Treg) and their anti-inflammatory actions. In this view, an inadequate microbial colonisation of the gut results in an imbalance between Treg cells and their effector targets, the different Th cells, and the subsequent deregulation of immune responses could promote inflammation, autoimmunity or the onset of atopies.[40,51,57-59] Experimental work in mice has demonstrated that crosstalk between the gut microbiota and the immune system is indeed obligatory for the generation of Tregs within the intestine and the avoidance of pathological intestinal inflammation.[60] The picture of immune regulation has also grown more complex due to the discovery of the IL-17-producing Th cells (Th17),[61] which are providing new insights into the cellular and molecular mechanisms of immunity and have been shown to be important in diseases that had classically been defined as Th1 or Th2-mediated.[55,62,63] In this context, different commensal microbes will induce the differentiation of naïve T cells into different subtypes with different roles. For instance, experimental work in mice has shown that *Bacteroides fragilis*[64] and *Clostridium* species belonging to phylogenetic groups IV and XIV[65] promote the differentiation of T cells into anti-inflammatory Tregs, while the segmented filamentous bacteria (SFB) induce the development of the pro-inflammatory Th17.[66]

Studies in mice have also provided specific results regarding how antibiotics affect the balance of T cell subtypes and the homeostasis of the immune system. In agreement with the roles of *Clostridium* species and SFB just described, treatment with vancomycin, an antibiotic that kills Gram-positive bacteria, reduces the numbers of Treg cells in the colon lamina propia, and impairs the induction of Th17 cells.[65] Moreover, administration of antibiotics during early life has been shown to be a determinant of allergic sensitisation. Administration of kanamycin to 3-week-old mice reduced Peyer's patch cellularity and induced skewing of immune responses towards Th2 (increased IgE and IgG1 and stimulated IL-4 production) while reducing Th1 responses (interferon-γ production). These changes could be reversed by colonisation with *Enterococcus faecalis* and attenuated by *Lactobacillus acidophilus*, but were exacerbated by *Bacteroides vulgatus*, underscoring the importance of specific types of bacteria in maintaining immune balance.[67] Similarly, 2-week-old mice treated with a cocktail of antibiotics had decreased expression of TLRs and produced cytokine profiles that maintained a Th2 phenotype.[68] These experiments clearly show that early antibiotic administration can bias immune development towards an atopy-prone state.

In addition to their effects on the balance of T cell subtypes, antibiotic-induced dysbioses are also likely to influence immunotolerance through their impact on other processes that affect the general inflammatory tone of the intestine. Among these, dysbioses can reduce the production of the non-inflammatory IgA that contributes to pathogen and allergen exclusion in the intestinal epithelia, mucus and lumen.[40,51] Importantly, metronidazole has been shown to reduce the intestinal expression of Muc2, the major component of the mucin layer,[69] and the ensuing thinning of this layer may increase contact between epithelial cells and the gut microbiota, thereby enhancing innate immune stimulation and elevating inflammation.

EFFECTS ON METABOLIC HEALTH

The gut microbiota is increasingly considered an important factor in the regulation of host metabolism, in particular as it relates to energy homeostasis and adiposity. This is not surprising, given that intestinal microbes consume non-digestible carbohydrates and produce short-chain fatty acids (SCFA), which play several important metabolic roles. SCFA modulate secretion of the hormone GLP1, which in turn improves insulin secretion,[70] and regulates fat deposition through interaction with G-protein-coupled receptors (GPCRs).[71] Intestinal microbes also convert primary bile acids, synthesised in the human liver, into secondary bile acids, which bind to the GPCR TGR5 to promote glucose homeostasis.[72]

Several metabolic disorders have recently been linked with disbalances of the gut microbiota. Notably, obesity has been shown to be associated with phylum-level changes in the gut microbiota, reduced bacterial diversity, and altered representation of bacterial genes and metabolic pathways, differences that endow the obesity–associated microbiota with an increased capacity to harvest energy from the diet.[73-75] This is in line with the fact that long-term exposure to antibiotics is associated with increased body mass index, both in humans[76-78] and in farm animals, where low-dose antibiotics have long been used to promote weight gain.[79] Moreover, recent work in mice has shown that early antibiotic exposure can cause obesity even with normal dietary intake.[80] Antibiotic use is therefore emerging as an important risk factor for the development of obesity.

Overweight and obesity can progress to metabolic syndrome, a complex of metabolic abnormalities leading to an increased risk for cardiovascular disease, fatty liver disease, steatohepatitis, and type 2 diabetes.[81] Although the pathophysiological mechanisms that lead from obesity to metabolic syndrome are still unclear, they likely include the generation of a state of chronic low-grade inflammation associated with excess adipose tissue, which seems to be at least partly mediated by the gut microbiota. In this respect, high-fat diets (HFD) have been shown to alter the gut microbiota of mice with an increase of lipopolysaccharide (LPS)-containing bacteria, which leads to higher amounts of this pro-inflammatory bacterial cell wall component in blood serum. Interestingly, continuous subcutaneous infusion of LPS, mimicking the HFD state, has been shown to induce some of the aspects of metabolic syndrome.[82] Similarly, influx into the portal vein of bacterial components agonistic of TLR4 and TLR9 promotes the progression of fatty liver disease to steatohepatitis by enhancing hepatic expression of the pro-inflammatory cytokine TNFα.[83] On the other hand, TLR5 deficiency results in a dysbiotic state that promotes metabolic syndrome signs, such as obesity, insulin resistance and dyslipidaemia, and transplantation of the gut microbiota from TLR5-deficient mice into germ-free recipients can transmit the phenotype, suggesting that the gut microbiota alone can mediate disease.[84] Moreover, wild-type mice containing the altered gut microbiota had higher intestinal levels of pro-inflammatory TNFα and IL-1β, suggesting that the transplanted gut microbiota did contribute to the observed metabolic disorders through the induction of intestinal inflammation. Because antibiotic use can lead to gut microbiota alterations that promote inflammation,[51,69,85] it could exacerbate the progression from obesity to metabolic syndrome.

CONCLUDING REMARKS

Antibiotic-induced dysbioses have a variety of negative effects on health, some of which can remain for long periods of time after antibiotic administration. Beyond admonishing against the unnecessary, excessive or inefficient use of antibiotics, this realisation should promote research into potential strategies to minimise the negative consequences of antibiotics when their administration is required. Promising approaches involve the use of probiotic bacteria or of bacterial ligands of innate immune receptors to re-establish the interactions impeded by the antibiotic-induced alterations of the original gut microbiota.[24] However, the effective display of such approaches will necessitate much further research into the manners in which specific bacteria interact with the different components of the immune system to maintain its balance.

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REFERENCES

1. Sekirov I et al. Gut microbiota in health and disease. Physiol Rev. 2010;90(3):859-904.

2. Collado MC et al. "Human Microbiome and Diseases: A Metagenomic Approach," Watson RR, Preedy VR (eds), Bioactive food as dietary interventions for liver and gastrointestinal disease (2013), San Diego:Academic Press. pp. 235-49.

3. Dethlefsen L et al. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. PLoS Biol. 2008;6(11):e280.

4. Dethlefsen L, Relman DA. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. Proc Natl Acad Sci USA. 2011;108(Suppl 1):4554-61.

5. De La Cochetiere MF et al. Resilience of the dominant human fecal microbiota upon short-course antibiotic challenge. J Clin Microbiol. 2005;43(11):5588-92.

6. Jernberg C et al. Long-term ecological impacts of antibiotic administration on the human intestinal microbiota. ISME J. 2007;1(1):56-66.

7. Antonopoulos DA et al. Reproducible community dynamics of the gastrointestinal microbiota following antibiotic perturbation. Infect Immun. 2009;77(6):2367-75.

8. Ubeda C et al. Vancomycin-resistant Enterococcus domination of intestinal microbiota is enabled by antibiotic treatment in mice and precedes bloodstream invasion in humans. J Clin Invest. 2010;120(12):4332-41.

9. Perez-Cobas AE et al. Gut microbiota disturbance during antibiotic therapy: a multi-omic approach. Gut. 2012;62(11):1591-601.

10. Hernandez E et al. Functional consequences of microbial shifts in the human gastrointestinal tract linked to antibiotic treatment and obesity. Gut Microbes. 2013;4(4):306-15.

11. Maurice CF et al. Xenobiotics shape the physiology and gene expression of the active human gut microbiome. Cell. 2013;152(1-2):39-50.

12. Wilcox MH. Gastrointestinal disorders and the critically ill. Clostridium difficile infection and pseudomembranous colitis. Best Pract Res Clin Gastroenterol. 2003;17(3):475-93.

13. Young VB, Schmidt TM. Antibiotic-associated diarrhea accompanied by large-scale alterations in the composition of the fecal microbiota. J Clin Microbiol. 2004;42(3):1203-6.

14. Song HJ et al. Antibiotic-associated diarrhea: candidate organisms other than Clostridium difficile. Korean J Intern Med. 2008;23(1):9-15.

15. Rupnik M et al. Clostridium difficile infection: new developments in epidemiology and pathogenesis. Nat Rev Microbiol. 2009;7(7):526-36.

16. Chen JW et al. Proteomic comparison of historic and recently emerged hypervirulent Clostridium difficile strains. J Proteome Res. 2013;12(3):1151-61.

17. Chang JY et al. Decreased diversity of the fecal Microbiome in recurrent Clostridium difficile-associated diarrhea. J Infect Dis. 2008;197(3):435-8.

18. Lawley TD et al. Antibiotic treatment of clostridium difficile carrier mice triggers a supershedder state, spore-mediated transmission, and severe disease in immunocompromised hosts. Infect Immun. 2009;77(9):3661-9.

19. Buffie CG et al. Profound alterations of intestinal microbiota following a single dose of clindamycin results in sustained susceptibility to Clostridium difficile-induced colitis. Infect Immun. 2012;80(1):62-73.

20. Gupta TP, Ehrinpreis MN. Candida-associated diarrhea in hospitalized patients. Gastroenterology. 1990;98(3):780-5.

21. Danna PL et al. Role of candida in pathogenesis of antibiotic-associated diarrhoea in elderly inpatients. Lancet. 1991;337(8740):511-4.

22. Levine J et al. Candida-associated diarrhea: a syndrome in search of credibility. Clin Infect Dis. 1995;21(4):881-6.

23. Krause R et al. Role of Candida in antibiotic-associated diarrhea. J Infect Dis. 2001;184(8):1065-9.

24. Ubeda C, Pamer EG. Antibiotics, microbiota, and immune defense. Trends Immunol. 2012;33(9):459-66.

25. Brandl K et al. Vancomycin-resistant enterococci exploit antibiotic-induced innate immune deficits. Nature. 2008;455(7214):804-7.

26. Vaishnava S et al. Paneth cells directly sense gut commensals and maintain homeostasis at the intestinal host-microbial interface. Proc Natl Acad Sci USA. 2008;105(52):20858-63.

27. Clarke TB et al. Recognition of peptidoglycan from the microbiota by Nod1 enhances systemic innate immunity. Nat Med. 2010;16(2):228-31.

28. Ichinohe T et al. Microbiota regulates immune defense against respiratory tract influenza A virus infection. Proc Natl Acad Sci USA. 2011;108(13):5354-9.

29. Dufour V et al. Effects of a short-course of amoxicillin/clavulanic acid on systemic and mucosal immunity in healthy adult humans. Int Immunopharmacol. 2005;5(5):917-28.

30. Manichanh C et al. Reduced diversity of faecal microbiota in Crohn's disease revealed by a metagenomic approach. Gut. 2006;55(2):205-11.

31. Vanderploeg R et al. Influences of intestinal bacteria in human inflammatory bowel disease. Infect Dis Clin North Am. 2010;24(4):977-93,ix.

32. Vanner S. The small intestinal bacterial overgrowth. Irritable bowel syndrome hypothesis: implications for treatment. Gut. 2008;57(9):1315-21.

33. Yamini D, Pimentel M. Irritable bowel syndrome and small intestinal bacterial overgrowth. J Clin Gastroenterol. 2010;44(10):672-5.

34. Durban A et al. Structural alterations of faecal and mucosa-associated bacterial communities in irritable bowel syndrome. Environ Microbiol Rep. 2012;4(2):242-7.

35. Tana C et al. Altered profiles of intestinal microbiota and organic acids may be the origin of symptoms in irritable bowel syndrome. Neurogastroenterol Motil. 2010;22(5):512-9, e114-5.

36. Mendall MA, Kumar D. Antibiotic use, childhood affluence and irritable bowel syndrome (IBS). Eur J Gastroenterol Hepatol. 1998;(1):59-62.

37. Hildebrand H et al. Early-life exposures associated with antibiotic use and risk of subsequent Crohn's disease. Scand J Gastroenterol. 2008;43(8):961-6.

38. Kuvaeva IB et al. Microecology of the gastrointestinal tract and the immunological status under food allergy. Nahrung. 1984;28(6-7):689-93.

39. Penders J et al. The role of the intestinal microbiota in the development of atopic disorders. Allergy. 2007;62(11):1223-36.

40. Penders J et al. Gut microbiota composition and development of atopic manifestations in infancy: the KOALA Birth Cohort Study. Gut. 2007;56(5):661-7.

41. Bjorksten B et al. The intestinal microflora in allergic Estonian and Swedish 2-year-old children. Clin Exp Allergy. 1999;29(3):342-6.

42. Sepp E et al. Intestinal microbiota and immunoglobulin E responses in 5-year-old Estonian children. Clin Exp Allergy. 2005;35(9):1141-6.

43. Sepp E et al. Intestinal microflora of Estonian and Swedish infants. Acta Paediatr. 1997;86(9):956-61.

44. Wang M et al. Reduced diversity in the early fecal microbiota of infants with atopic eczema. J Allergy Clin Immunol. 2008;121(1):129-34.

45. Bisgaard H et al. Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age. J Allergy Clin Immunol. 2011;128(3):646-52 e1-5.

46. Abrahamsson TR et al. Low diversity of the gut microbiota in infants with atopic eczema. J Allergy Clin Immunol. 2012;129(2):434-40.e1-2.

47. Gosalbes MJ et al. Meconium microbiota types dominated by lactic acid or enteric bacteria are differentially associated with maternal eczema and respiratory problems in infants. Clin Exp Allergy. 2013;43(2):198-211.

48. Jedrychowski W et al. The prenatal use of antibiotics and the development of allergic disease in one year old infants. A preliminary study. Int J Occup Med Environ Health. 2006;19(1):70-6.

49. Stensballe LG et al. Use of antibiotics during pregnancy increases the risk of asthma in early childhood. J Pediatr. 2013;162(4):832-8.e3.

50. Russell AR, Murch SH. Could peripartum antibiotics have delayed health consequences for the infant? BJOG. 2006;113:758-65.

51. Rautava S et al. The hygiene hypothesis of atopic disease--an extended version. J Pediatr Gastroenterol Nutr. 2004;38(4):378-88.

52. Romagnani S. The increased prevalence of allergy and the hygiene hypothesis: missing immune deviation, reduced immune suppression, or both? Immunology. 2004;112(3):352-63.

53. Sjogren YM et al. Altered early infant gut microbiota in children developing allergy up to 5 years of age. Clin Exp Allergy. 2009;39(4):518-26.

54. Jutel M, Akdis CA. T-cell subset regulation in atopy. Curr Allergy Asthma Rep. 2011;11(2):139-45.

55. Oboki K et al. Th17 and allergy. Allergol Int. 2008;57(2):121-34.

56. Abbas AK. Die and let live: eliminating dangerous lymphocytes. Cell. 1996;84(5):655-7.

57. Rook GA, Brunet LR. Microbes, immunoregulation, and the gut. Gut. 2005;54(3):317-20.

58. Yazdanbakhsh M, Kremsner PG, van Ree R. Allergy, parasites, and the hygiene hypothesis. Science. 2002;296(5567):490-4.

59. Wills-Karp M, Santeliz J, Karp CL. The germless theory of allergic disease: revisiting the hygiene hypothesis. Nat Rev Immunol. 2001;1(1):69-75.

60. Strauch UG et al. Influence of intestinal bacteria on induction of regulatory T cells: lessons from a transfer model of colitis. Gut. 2005;54(11):1546-52.

61. Infante-Duarte C et al. Microbial lipopeptides induce the production of IL-17 in Th cells. J Immunol. 2000;165(11):6107-15.

62. Murphy KM. In search of the CTD. Nat Immunol. 2003;4(7):645.

63. Nakae S et al. Antigen-specific T cell sensitization is impaired in IL-17-deficient mice, causing suppression of allergic cellular and humoral responses. Immunity. 2002;17(3):375-87.

64. Round JL, Mazmanian SK. Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. Proc Natl Acad Sci USA. 2010;107(27):12204-9.

65. Atarashi K et al. Induction of colonic regulatory T cells by indigenous Clostridium species. Science. 2011;331(6015):337-41.

66. Ivanov et al. Induction of intestinal Th17 cells by segmented filamentous bacteria. Cell. 2009;139(3):485-98.

67. Sudo N et al. An oral introduction of intestinal bacteria prevents the development of a long-term Th2-skewed immunological memory induced by neonatal antibiotic treatment in mice. Clin Exp Allergy. 2002;32(7):1112-6.

68. Dimmitt RA et al. Role of postnatal acquisition of the intestinal microbiome in the early development of immune function. J Pediatr Gastroenterol Nutr. 2010;51(3):262-73.

69. Wlodarska M et al. Antibiotic treatment alters the colonic mucus layer and predisposes the host to exacerbated Citrobacter rodentium-induced colitis. Infect Immun. 2011;79(4):1536-45.

70. Tolhurst G et al. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. Diabetes. 2012;61(2):364-71.

71. Samuel BS et al. Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. Proc Natl Acad Sci USA. 2008;105(43):16767-72.

72. Thomas C et al. TGR5-mediated bile acid sensing controls glucose homeostasis. Cell Metab. 2009;10(3):167-77.

73. Backhed F et al. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci USA. 2004;101(44):15718-23.

74. Turnbaugh PJ et al. A core gut microbiome in obese and lean twins. Nature. 2009;457(7228):480-4.

75. Turnbaugh PJ et al. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006;444(7122):1027-31.

76. Thuny F et al. Vancomycin treatment of infective endocarditis is linked with recently acquired obesity. PLoS One. 2010;5(2):e9074.

77. Ajslev TA et al. Childhood overweight after establishment of the gut microbiota: the role of delivery mode, pre-pregnancy weight and early administration of antibiotics. Int J Obes (Lond). 2011;35(4):522-9.

78. Angelakis E et al. The relationship between gut microbiota and weight gain in humans. Future Microbiol. 2012;7(1):91-109.

79. Burch DG. Is it time to ban all antibiotics as animal growth-promoting agents? Lancet. 1996;348(9039):1455. Author reply 1455-6.

80. Cho I et al. Antibiotics in early life alter the murine colonic microbiome and adiposity. Nature. 2012;488(7413):621-6.

81. Emanuela F et al. Inflammation as a link between obesity and metabolic syndrome. J Nutr Metab. 2012;2012:476380.

82. Cani PD et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes. 2007;56(7):1761-72.

83. Henao-Mejia J et al. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. Nature. 2012;482(7384):179-85.

84. Vijay-Kumar M et al. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. Science. 2010;328(5975):228-31.

85. Jenq RR et al. Regulation of intestinal inflammation by microbiota following allogeneic bone marrow transplantation. J Exp Med. 2012 May 7;209(5):903-11.

MANAGING ULCERATIVE COLITIS: THE GUIDELINES AND BEYOND

Mitchell RKL Lie, C Janneke van der Woude

Department of Gastroenterology, Erasmus University Hospital, Rotterdam, the Netherlands

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ABSTRACT

Management guidelines offer clinicians clear, evidence-based and often succinct treatment advice. For ulcerative colitis these guidelines describe the use of 5-ASA, corticosteroids, thiopurines, cyclosporine, and anti-TNFα therapies. However, guidelines do have some drawbacks, mainly a lack of concrete advice concerning patients resistant to these aforementioned therapies. This review gives a short overview of current guidelines and addresses treatment alternatives for conventional therapies.

Keywords: Ulcerative colitis, management, therapy, 5-ASA, corticosteroids, azathioprine, 6-mercaptopurine, 6-thioguanine, cyclosporine, tacrolimus, methotrexate, mycophenolate mofetil, infliximab, adalimumab, golimumab, vedolizumab.

INTRODUCTION

The management of ulcerative colitis (UC) remains challenging to even the most seasoned clinician. This is partly due to the non-elucidated aetiology of the disease. Periodically updated guidelines are valuable instruments that aid clinicians in decision-making. However, the management of UC at an individual level remains challenging due to highly variable disease presentations that are not specifically covered by the guidelines. Decision-making can be difficult for patients intolerant to conventional therapy, or with treatment-resistant disease limited to only the rectum. Also, a patient's preference for certain treatments can result in more complicated decision-making, for example when patients refuse certain drugs or surgery.

In this review we will summarise the latest guidelines on the management of UC. Additionally, treatment options and evidence for patients that have exhausted the therapies suggested by the guidelines will be discussed and a strategy will be proposed for this particular subgroup. Furthermore, the limited evidence of several new biological therapies close to registration and approval will be examined.

THERAPIES FOR ACUTE REMISSION INDUCTION

The choice of therapy depends on disease severity and localisation. To properly describe severity and localisation, several classification systems exist. Most often the Mayo score or the Truelove and Witts' index is used to classify severity, whereas localisation is usually anatomically described as proctitis (rectum only), left-sided (beyond the rectum but distal of the splenic flexure), or extensive (extending beyond splenic flexure). Below, the appropriate conventional treatments are summarised. The 2012 European Crohn's and Colitis Organisation (ECCO) guidelines on UC give more thorough recommendations in different situations.[1]

Proctitis

Topical 5-ASA therapy is the first-line therapy for proctitis. There is evidence for topical treatment only,[2-12] with some evidence showing that topical 5-ASA treatment is superior to oral 5-ASA treatment alone.[13] Topical steroid therapy has been found to be inferior for remission induction[14] and should therefore be used as a second-line therapy in case of 5-ASA intolerance.

Left-Sided Disease

A combination of oral and topical 5-ASA has proven to be more effective than either agent alone in the treatment of left-sided UC.[15-18] If this fails, oral steroids might be added.

Extensive Disease

Combined oral plus topical 5-ASA remains the first-line of treatment. If this therapy fails, oral steroids can be added.[19-23] If steroid dependence occurs, thiopurine treatment is recommended.[24]

Severe Disease

Severe disease is potentially life-threatening and in most cases requires hospital admission and immediate treatment. All guidelines recommend high-dose intravenous glucocorticoids as the first treatment modality, even though only limited evidence exists.[25-27] Early consideration of salvage treatments is of great importance as a precautionary measure as the patient may not respond to steroid treatment.

Intravenous Steroid-Refractory Severe Disease

Intravenous steroid-refractory disease leaves clinicians with limited drug therapies. Salvage therapy should not be initiated simply to delay surgery, as such delays will lead to greater morbidity at surgery.[28] If clinical and biochemical parameters allow an attempt at salvage, the guideline recommends cyclosporine, infliximab or tacrolimus. High quality prospective evidence exists for the use of cyclosporine,[27,29-31] confirmed by several retrospective studies.[32-34] There is also prospective evidence[31,35-37] and some retrospective evidence[34] for infliximab as a rescue therapy. The prospective evidence for tacrolimus is less extensive,[38-40] containing heterogeneous populations and the use of tacrolimus is therefore not as strongly recommended by the guideline.

There is limited evidence for using infliximab as a rescue therapy to cyclosporine, or vice-versa.[41,42] The guideline recommends such a third-line therapy only in select cases treated by a multi-disciplinary team in specialist centres.

TREATMENTS AND ALTERNATIVES FOR STEROID-DEPENDENT DISEASE

Though intravenous steroid-refractory disease represents the most severe cases of UC, this presentation is relatively rare. In contrast, it is more common to see outpatients who reach remission but either fail to taper their steroids or relapse soon after tapering, making them steroid-dependent. In the following paragraph several options for the treatment of steroid-dependent disease and their respective evidence will be discussed.

Thiopurines

A prospective study[43] has shown that azathioprine (AZA) and its metabolite 6-mercaptopurine (6-MP) are highly effective in achieving steroid-free remission, with persistent long-term results found in observational studies.[44]

Anti-TNFα

In case of failure or intolerance to thiopurines, anti-TNFα therapy is considered the next step. Several large trials[45] and a Cochrane meta-analysis[46] have conclusively proven the efficacy of infliximab in this setting. Though less extensively studied,[47,48] adalimumab has also shown efficacy in steroid-dependent disease and in patients intolerant to thiopurine treatment.

UNCONVENTIONAL THERAPIES

If conventional therapies fail, colectomy becomes a valid treatment option for patients with UC. Clinical experience shows a profound difference in acceptability of colectomy in hospitalised patients compared with outpatients, though no formal studies have examined this issue. It is not uncommon for outpatients to refuse colectomy, despite being informed of the possible benefits of such intervention. In these situations a clinician may need to resort to either enrollment in clinical trials or initiation of an unconventional therapy in the hope of controlling a patient's symptoms. The provided algorithm (Figure 1) may help clinicians in their decision-making regarding these therapies, which are described in more detail below.

Therapy-Resistant Proctitis

A subset of patients with disease limited to the rectum is surprisingly treatment-resistant to topical 5-ASA and/or topical steroid therapies. This may present clinicians with a treatment dilemma: escalate to systemic therapies, with all associated adverse effects, or accept the limited disease localisation. There is a paucity of prospective controlled trials within this patient subgroup.

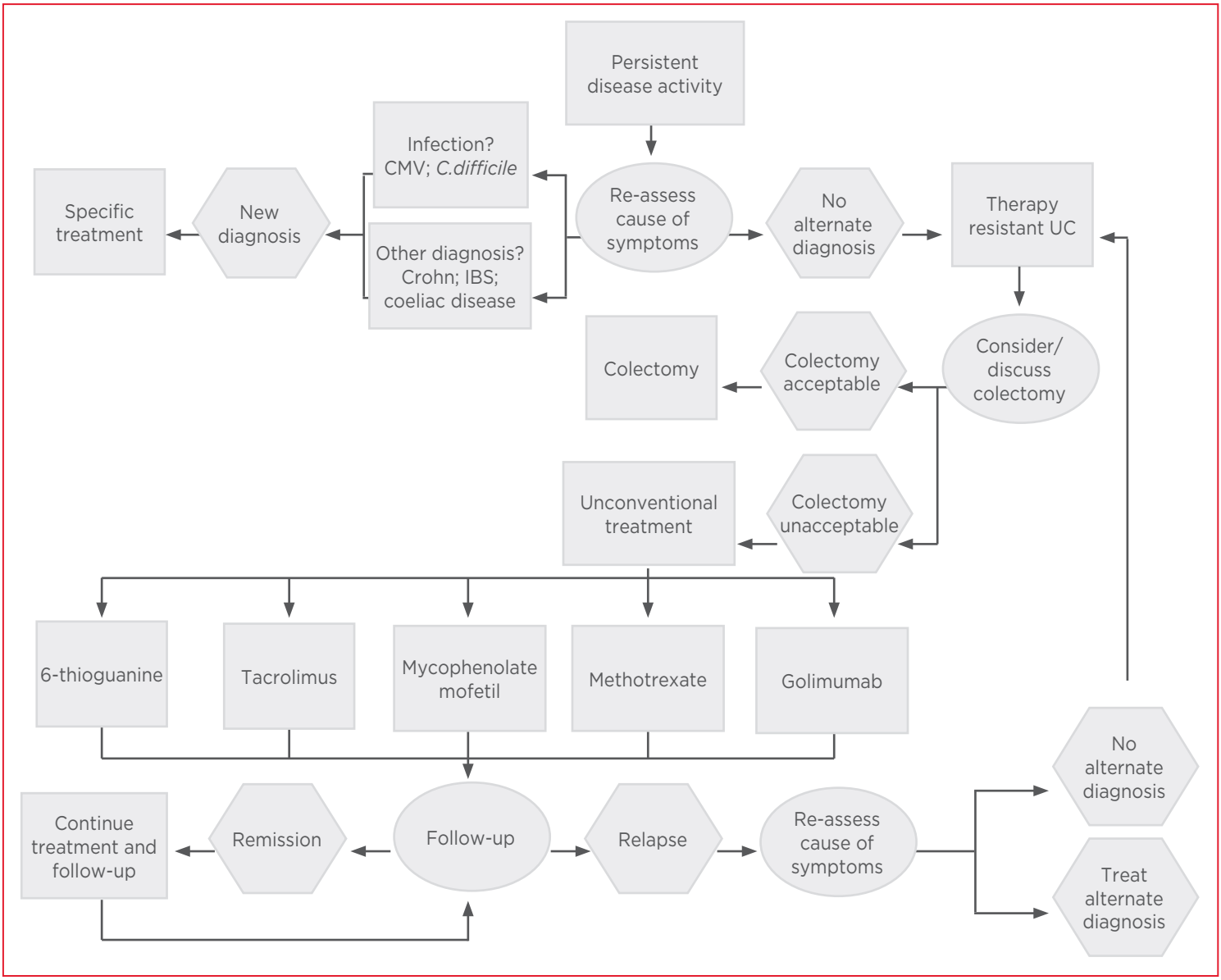

Figure 1. Management algorithm for therapy-resistant ulcerative colitis.
UC: ulcerative colitis; CMV: cytomegalovirus; IBS: irritable bowel syndrome.

There is only one randomised, placebo-controlled trial remotely addressing this issue.[49] This study investigated the efficacy of cyclosporine enemas in left-sided disease (disease extent ranging from 10 to 60 cm ab ani). No significant difference in remission rate between cyclosporine and placebo was found.

Two open-label pilot studies investigated the efficacy of topical tacrolimus for treatment-resistant proctitis. The first,[50] applied tacrolimus ointment in ulcerative proctitis patients who failed previous 5-ASA, steroid, immunosuppressant, and infliximab therapy. 75% (6 out of 8) achieved remission after 8 weeks, with reduction or cessation of steroid usage in five of the responders. The second,[51] treated 12 patients with ulcerative proctitis resistant to topical 5-ASA and/or topical steroid therapy. This study used tacrolimus suppositories and assessed efficacy after 4 weeks of treatment. Clinical remission was achieved in 83% (10 out of 12) with complete endoscopic healing in 33% (4 out of 12). These promising pilots warrant further investigation of topical tacrolimus in treatment-resistant ulcerative proctitis.

Even retrospective data are scarce. One study[52] retrospectively investigated the efficacy of infliximab in patients with proctitis resistant to at least 5-ASA and steroids. Clinical response was seen in 85% (11 out of 13) after infliximab induction therapy. Two patients suffered from adverse events. Other retrospective studies[53-55]

regarding infliximab contain only a few subjects with proctitis, and their response is not individually reported.

Mycophenolate Mofetil

No randomised studies have been performed, but the results of one retrospective and three open-label prospective studies have been published. The first study[56] retrospectively examined the effectiveness of mycophenolate mofetil (MMF) in 70 steroid-dependent inflammatory bowel disease (IBD) patients, of which 19 had UC. After an unclear treatment time (the average treatment time amongst all study subjects was 28 months), 35% (6 out of 17) of UC patients was in steroid-free remission. 65% (11 out of 17) failed to respond to MMF or were intolerant.

The three prospective studies consist of two uncontrolled, open-label studies, and one unblinded pilot study. The first open-label study[57] examined 24 IBD patients, of which 13 had UC with moderate-to-severe steroid-dependent disease. Patients were treated with combined MMF and high-dose steroids with tapering. In the first 3 months, 46% (6 out of 13) of patients achieved remission, but after steroids were tapered, the disease relapsed in all UC patients. The other open-label study[58] treated 14 patients with IBD resistant to conventional therapy. They included five patients with UC (or IBD unclassified), all of which were steroid-dependent and intolerant to thiopurines. One patient suffered from side-effects and ceased MMF treatment; the other four reached remission at 8 weeks and ceased steroid treatment. Follow-up at 12 months showed a maintained remission in 67% of all patients, but the exact data for UC patients at that time point are not reported.

Lastly, in the only controlled study[59] MMF was compared to azathioprine in 24 UC patients. Both groups received steroids in a tapering dose. Notably, this study excluded patients with current steroid usage. After 4 weeks of treatment, 67% (8 out of 12) in the MMF group reached remission and five remained in remission throughout the whole follow-up period of 1 year. However during the entire study, the remission rates were higher in the azathioprine group than in the MMF group, though no significance value is provided by the authors.

Methotrexate

Few prospective studies have been performed on methotrexate (MTX) in UC. One study in 1996[60] examines the effectiveness of MTX versus placebo in steroid-dependent UC. No difference in remission rates was found (47% in the MTX group), which is similar to the results of several case series[61-63] (45-54%). However it has been argued[64-65] that the studied dose of 12.5 mg/week is considerably lower than the 'modern' dose of 20 to 25 mg/week.

Upcoming results of the French METEOR study and the North American MERIT-UC study may shed some light on the use of MTX in UC. Both investigate the effectiveness of MTX 25 mg/week for remission induction in treatment-resistant and/or steroid-dependent UC. It should be noted that whilst according to www.clinicaltrials.gov the MERIT-UC study is currently recruiting, the METEOR study already ended in November 2010, but as of yet no results have been published.

Tacrolimus

Several retrospective studies[66-73] have analysed the effects of tacrolimus on severe, therapy-resistant UC. Outcome parameters, concomitant medication, tacrolimus dosage, and target trough levels varied amongst these studies. However, all studies show a high clinical response rate, varying between 61% and 90%. Reported clinical remission rates vary between 33% and 72%.

The only randomised, controlled trial[38] concerning tacrolimus in UC randomised 62 patients with steroid refractory, moderate-to-severe UC. Changes in the tacrolimus dose were made to achieve a target trough level of 10-15 ng/mL. This study shows a 50% clinical response at 2 weeks, with a clinical remission rate of 9% (3 out of 32), with greater response amongst patients who reached the target trough level. After a 2 week open-label extension period, the clinical remission rate increased to 29% (6 out of 21).

6-Thioguanine

6-Thioguanine (6-TG) is a metabolite of 6-mercaptopurine. Because of polymorphisms in the enzyme thiopurine methyltransferase, the conversion of 6-MP to 6-TG can differ markedly between patients. Directly administering 6-TG should therefore remove dosing issues whilst in theory achieving similar results to AZA and 6-MP treatment.

However there is little published data that study 6-TG treatment directly. Of additional interest is the use of 6-TG in patients with intolerance to AZA or 6-MP. An open-label pilot study was performed in 49 patients with Crohn's disease, of whom 23 patients had pancreatitis after AZA or 6-MP administration.[74] None of these patients had recurrence of their pancreatitis after switching to 6-TG.

A database analysis[75] was performed regarding UC patients receiving 6-TG after becoming intolerant to conventional thiopurine treatment and/or being steroid-dependent. 46 UC patients were examined, of which 83% (37 out of 46) were on steroids when 6-TG therapy was initiated. 80% (37 out of 46) of patients remained in remission after a median follow-up time of 22.4 months, 13% (6 out of 46) were intolerant, and the remaining 7% (3 out of 46) failed therapy and underwent colectomy. The amount of patients in steroid-free remission is not described.

A prospective, open-label study[76] treated 16 UC outpatients who had steroid-dependent or refractory disease. After 3 months, 31% (5 out of 16) had complete response, and 38% (6 out of 16) a partial response.

The measurement of 6-TG levels in the setting of monitoring AZA and 6-MP therapy has been studied extensively and has been found to be useful in meta-analyses.[77] If these results are extrapolated to direct treatment with 6-TG, it is likely that the clinical efficacy of 6-TG is similar to AZA and 6-MP treatment, as long as sufficient serum levels are achieved.

Summary Regarding Disease Resistant to Conventional Therapies

When treating patients with UC resistant to conventional therapies, the first step is to ensure that it is indeed the UC that is causing the symptoms. Critical re-assessment of the patient to rule out any other pathology is highly important. Secondly, good communication is key since the 'rescue' therapies described above have low remission rates and only weak supporting evidence. Patients should be well informed on the potential benefits and risks of these agents. Specifically, patients should be aware that failure of these therapies will increase the likelihood of requiring colectomy.

Figure 1 summarises our recommendations, whilst Table 1 shows recommended dosage, laboratory tests, and contraindications. 6-TG and tacrolimus have the highest reported remission rates; therefore, we would recommend these agents over MMF, MTX or LDN. The other three agents are still useful in specific circumstances, for instance LDN is the most suitable agent for females who wish to become pregnant.

Table 1. Recommended dosage, laboratory tests, and absolute contraindications for 6-thioguanine, tacrolimus, mycophenolate mofetil, and methotrexate.

Agent	Dosage	Contraindications	Laboratory and functional tests		Comments
			Preliminary	Follow-up	
6-thioguanine	OD, oral, 0,3 mg/kg	Liver insufficiency Pregnancy	CBC, LF, RF	CBC, LF	Consider TPMT enzyme activity testing Reduce dose in renal impairment Reduce dose if concomitant allopurinol
Tacrolimus	OD, oral, 0,1 mg/kg	Liver insufficiency	ECG, CBC, LF, RF	CBC, LF, RF, TL	Aim for trough level 4-8 ng/mL
Mycophenolate mofetil	BD, oral, 500-1000mg	Pregnancy	CBC, LF, RF	CBC, LF, RF	Adjust dose based on CBC
Methotrexate	QWK, SC, 25 mg Reduce to QWK 15 mg after 12 weeks	Renal impairment (GFR <20 mL/min) Pregnancy	CBC, LF, RF	CBC, LF, RF	Also prescribe QWK 5 mg folic acid Adjust dose based on CBC

OD: once daily; BD: twice daily; QWK: once weekly; SC: subcutaneous; GFR: glomeruler filtration rate; CBC: complete blood count; LF: liver function; RF: renal function; TL: trough level; TPMT: thiopurine methyltransferase.

We strongly recommend that all the above drug treatments should be accompanied by close follow-up in order to detect treatment failure in a timely fashion. Laboratory markers such as faecal calprotectin, reflecting intestinal inflammation,[78,79] may aid in the follow-up process. In case of treatment failure or clinical deterioration, re-assessment should ensue, after which optimising therapy, switching therapy or, if necessary, colectomy should follow.

FUTURE THERAPIES

A search in the U.S. National Institutes of Health clinical trial database (http://clinicaltrials.gov) using the term 'ulcerative colitis' yields 169 planned or active studies. 29 of these studies involve new compounds, which reflect the continuing interest of many pharmaceutical companies regarding treatment for UC. These compounds are still only known by their study names and mostly involve Phase I and Phase II studies, with no results currently available on the website. Amongst these drug candidates are OKT-3 (an oral anti CD-3 agent), ASP3291 (a melanocortin receptor agonist), KRP203 (a sphingosine-1-phospate receptor modulator), GWP42003 (a cannabinoid), AMG181 (an α4β7 integrin antibody), HE3286 (a synthetic steroid derivative), GL1001 (an ACE-2 inhibitor), and MDX1100 (an CLCL10 antibody). It is anticipated that their role in UC will become clear in the near future.

Not all new and promising therapies live up to our expectations. For instance, basiliximab, daclizumab and visilizumab were promising in uncontrolled pilot studies,[80-84] but eventually showed identical remission rates to placebo in randomised controlled trials.[85-87]

Golimumab

Golimumab is a fully human antibody against TNFα. At the Digestive Disease Week, 2012 (DDW 2012), the initial results of the PURSUIT-SC trial regarding golimumab in UC were presented. Recently the complete article on this two-part, randomised, double-blind, placebo controlled Phase II-III study has been published.[88] A total of 1,064 patients were included, 291 in the Phase II dose-ranging study, 774 in the Phase III, efficacy study. All patients had moderate-to-severe UC and an inadequate or failed response to at least one conventional therapy. The efficacy study evaluated clinical response after 6 weeks of treatment which was achieved in 53% (275 out of 515) of the golimumab groups versus 30% (76 out of 256) of the placebo group. Clinical remission at 6 weeks was 18% (94 out of 515) for the golimumab groups versus 6% (16 out of 256) for the placebo group.

At least one study is planned to examine the efficacy in paediatric patients, whilst another study in Japan is recruiting patients. These studies will address the reproducibility of the results found in the PURSUIT-SC study, though its results have already led to FDA approval for golimumab in moderate-to-severe UC in May 2013.

Vedolizumab

Vedolizumab is an antibody to the α4β7 integrin heterodimer complex. Three studies have been published on its efficacy in UC. The first study[89] reported results of a randomised controlled trial performed in 181 patients. Patients were either untreated or had only received 5-ASA therapy. Vedolizumab or placebo was administered on day 1 and day 29. Clinical response rates were 66% and clinical remission was achieved in 33% at 6 weeks of follow-up.

Two other studies[90,91] on vedolizumab were a randomised, controlled dose-ranging study, and an open-label extension of the first, with additional enrollment of treatment-naïve patients. In the controlled trial 47 patients with moderate, but not steroid-resistant, UC participated and medication or placebo was administered on day 1, 15, 29, and 85. Clinical response at 16 weeks was 60% to 80% (depending on dose). Clinical remission is reported as varying from 53% to 79% between day 29 and 253, compared with 25% to 50% in the placebo group. The study was underpowered for assessment of clinical outcome. The open-label extension study involved 72 patients with UC who were administered vedolizumab on day 1, 15, 43, followed by maintenance dose every 8 weeks. After 70 weeks of follow-up, clinical response was achieved in 92% and remission in 77% of patients with moderate-to-severe UC.

Recently the results of the GEMINI study, a multi-centre, randomised, double-blind, placebo-controlled trial were published.[92] This study involved two phases, with 895 patients in the induction and maintenance phase combined. Notably, patients had active disease and had

failed previous glucocorticoid, immunosuppressive or anti-TNFα therapy, though disease limited to the rectum was an exclusion criterion. After 6 weeks, coinciding with the end of the induction phase, vedolizumab showed a statistically significant 47% clinical response rate compared with 26% for placebo. The maintenance phase ended after 52 weeks, again showing a significant difference in clinical remission rates with 42% and 45% for vedolizumab in different doses, compared with 16% for placebo.

No current trials on vedolizumab were identified, but a request for FDA approval was filed in June 2013, most likely based on the results of the abovementioned studies.

Tofacitinib

Tofacitinib is an oral inhibitor of Janus kinase (JAK) 1, 2 and 3, and its effect should result in reduction of interleukin 2, 4, 7, 9, 15, and 21. The results of a large, multicentre, randomised, double-blind, placebo-controlled trial were published in 2012,[93] examining the efficacy of tofacitinib in patients with active UC. A total of 194 patients were randomised between five groups, one placebo group and four groups with different tofacitinib dosage (0.5 mg, 3 mg, 10 mg, and 15 mg twice daily). 34% of patients were using concomitant steroids, whilst 27% were steroid-resistant and 19% had failed anti-TNF therapy.

Significant difference in clinical remission was seen in the 3 mg, 10 mg, and 15 mg groups compared with placebo, with remission rates of 33%, 48%, 41% compared with 10%, respectively. Endoscopic remission showed similar significant differences, with 18%, 30%, 27% compared with 2% in the placebo group.

Regarding clinical and endoscopic response, only the highest tofacitinib dose showed a significant difference compared with placebo. Clinical response was 78% compared with 42%, whilst endoscopic response was 78% versus 46%.

Currently, the OCTAVE study is recruiting UC patients to analyse the efficacy in moderate-to-severely acute UC, resistant to at least corticosteroids, azathioprine or anti-TNF therapy. It consists of a remission induction phase, examining efficacy at 8 weeks, and is followed by a long-term follow-up study of 52 weeks.

CONCLUSION

In this paper we have reviewed the most recent guidelines by the ECCO on the treatment of UC. The proper evidence-based approach is described extensively in the guidelines, and we underscore its usefulness in clinical practice. Nevertheless, it remains challenging for clinicians to extrapolate the results obtained in clinical trials to individual patients.

When patients become resistant to conventional therapies, the situation moves beyond the guidelines, and it is for these situations that we offer the treatment algorithm described above. Of utmost importance remains the individualised and tailored approach, based on the patient's preference, the clinician's preference, and the availability of therapies. The choice of these unconventional therapies should be made in conjunction with the patient, underscoring the need for clear communication between clinician and patient, regarding the pros and cons of each treatment modality.

Finally, though the primary aim of these therapies is the induction and maintenance of remission, and subsequently the avoidance of surgery, one could also consider these agents as a bridge to novel treatments, either those substances currently awaiting regulatory approval or those in the last stage of their development.

REFERENCES

1. Dignass A et al. Second European evidence-based Consensus on the diagnosis and management of ulcerative colitis: Current management. J Crohns Colitis. 2012;6:991-1030.
2. Baron JH et al. Sulphasalazine and salicylazosulphadimidine in ulcerative colitis. Lancet. 1962;1:1094–6.
3. Dick AP et al. Controlled trial of sulphasalazine in the treatment of ulcerative colitis. Gut. 1964;5:437–42.
4. Hetzel DJ et al. Azodisalicylate (olsalazine) in the treatment of active ulcerative colitis. A placebo controlled trial and assessment of drug disposition. J Gastroenterol Hepatol. 1986;1:257–66.
5. Schroeder KW et al. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987;317:1625–9.
6. Miner P et al. Multicenter trial of Pentasa for active ulcerative colitis. Gastroenterology. 1991;100(Suppl):A231.

7. Sninsky CA et al. Oral mesalamine (Asacol) for mildly to moderately active ulcerative colitis. A multicenter study. Ann Intern Med. 1991;115:350–5.

8. Hanauer S et al. Mesalamine capsules for treatment of active ulcerative colitis: results of a controlled trial. Am J Gastroenterol. 1993;88:1188–97.

9. Kamm MA et al. Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. Gastroenterology. 2007;132:66–75.

10. Lichtenstein GR et al. Effect of once- or twice-daily MMX mesalamine (SPD476) for the induction of remission of mild to moderately active ulcerative colitis. Clin Gastroenterol Hepatol. 2007;5:95–102.

11. Scherl EJ et al. Safety and efficacy of a new 3.3 g b.i.d. tablet formulation in patients with mild-to-moderately-active ulcerative colitis: a multicenter, randomized, double-blind, placebo-controlled study. Am J Gastroenterol. 2009;104:1452–9.

12. Ito H et al. Direct comparison of two different mesalamine formulations for the induction of remission in patients with ulcerative colitis: a double-blind randomized study. Inflamm Bowel Dis. 2010;16:1567–74.

13. Gionchetti P et al. Comparison of oral with rectal mesalazine in the treatment of ulcerative proctitis. Dis Colon Rectum. 1998;41:93–7.

14. Marshall JK, Irvine EJ. Rectal corticosteroids versus alternative treatments in ulcerative colitis: a meta-analysis. Gut. 1997;40:775–81.

15. Fruhmorgen P, Demling L. On the efficacy of ready-made-up commercially available salicylazosulphapyridine enemas in the treatment of proctitis, proctosigmoiditis and ulcerative colitis involving rectum, sigmoid, and descending colon. Hepatogastroenterology. 1980;27:473–6.

16. Vecchi M et al. Oral versus combination mesalazine therapy in active ulcerative colitis: a double-blind, double-dummy, randomized multicentre study. Aliment Pharmacol Ther. 2001;15:251–6.

17. Marteau P et al. Combined oral and enema treatment with Pentasa (mesalazine) is superior to oral therapy alone in patients with extensive mild/moderate active ulcerative colitis: a randomised, double blind, placebo controlled study. Gut. 2005;54:960–5.

18. Safdi M et al. A double-blind comparison of oral versus rectal mesalamine versus combination therapy in the treatment of distal ulcerative colitis. Am J Gastroenterol. 1997;92:1867–71.

19. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; preliminary report on a therapeutic trial. Br Med J. 1954;2:375–8.

20. Angus P et al. Oral fluticasone propionate in active distal ulcerative colitis. Gut. 1992;33:711–4.

21. Bossa F et al. Erythrocyte-mediated delivery of dexamethasone in patients with mild-to-moderate ulcerative colitis, refractory to mesalamine: a randomized, controlled study. Am J Gastroenterol. 2008;103:2509–16.

22. Lennard-Jones JE et al. An assessment of prednisone, salazopyrin, and topical hydrocortisone hemisuccinate used as out-patient treatment for ulcerative colitis. Gut. 1960;1:217–22.

23. Rizzello F et al. Oral beclomethasone dipropionate in patients with mild to moderate ulcerative colitis: a dose-finding study. Adv Ther. 2001;18:261–71.

24. Ardizzone S et al. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. Gut. 2006;55:47–53.

25. Bossa F et al. Continuous infusion versus bolus administration of steroids in severe attacks of ulcerative colitis: a randomized, double-blind trial. Am J Gastroenterol. 2007;102:601–8.

26. Campieri M et al. Oral beclometasone dipropionate in the treatment of extensive and left-sided active ulcerative colitis: a multicentre randomised study. Aliment Pharmacol Ther. 2003;17(12):1471-80.

27. D'Haens G et al. Intravenous cyclosporine versus intravenous corticosteroids as single therapy for severe attacks of ulcerative colitis. Gastroenterology. 2001;120(6):1323-9.

28. Randall J et al. Delayed surgery for acute severe colitis is associated with increased risk of postoperative complications. Br J Surg. 2010;97:404–9.

29. Van Assche G et al. Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. Gastroenterology. 2003;125:1025–31.

30. Lichtiger S et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Engl J Med. 1994;330(26):1841-5.

31. Laharie D et al. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. Lancet. 2012;380(9857):1909-15.

32. Actis GC et al. Colectomy rate in steroid-refractory colitis initially responsive to cyclosporin: a long-term retrospective cohort study. BMC Gastroenterol. 2007;7:13.

33. Dean KE et al. Infliximab or cyclosporine for acute severe ulcerative colitis: a retrospective analysis. J Gastroenterol Hepatol. 2012;27(3):487-92.

34. Sjöberg M et al. Infliximab or cyclosporine as rescue therapy in hospitalized patients with steroid-refractory ulcerative colitis: a retrospective observational study. Inflamm Bowel Dis. 2012;18(2):212-8.

35. Järnerot G et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. Gastroenterology. 2005;128(7):1805-11.

36. Sands BE et al. Infliximab in the treatment of severe, steroid-refractory ulcerative colitis: a pilot study. Inflamm Bowel Dis. 2001;7:83–8.

37. Lees CW et al. A retrospective analysis of the efficacy and safety of infliximab as rescue therapy in acute severe ulcerative colitis. Aliment Pharmacol Ther. 2007;26:411–9.

38. Ogata H et al. A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis. Gut. 2006;55:1255–62.

39. Fellermann K et al. Response of refractory colitis to intravenous or oral Tacrolimus (FK506). Inflamm Bowel Dis. 2002;8:317–24.

40. Hogenauer C et al. Effect of oral tacrolimus (FK 506) on steroid-refractory moderate/severe ulcerative colitis. Aliment Pharmacol Ther. 2003;18:415–23.

41. Chaparro M et al. Infliximab salvage therapy after failure of ciclosporin in corticosteroid-refractory ulcerative colitis: a multicentre study. Aliment Pharmacol Ther. 2012;35(2):275-83.

42. Leblanc S et al. Successive treatment with cyclosporine and infliximab in steroid-refractory ulcerative colitis. Am J Gastroenterol. 2011;106(4):771-7.

43. Ardizzone S et al. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. Gut. 2006;55:47–53.

44. Chebli LA et al. Azathioprine maintains long-term steroid-free remission through 3 years in patients with steroid-dependent ulcerative colitis. Inflamm Bowel Dis. 2010;16:613–9.

45. Rutgeerts P et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353:2462–76.

46. Lawson MM et al. Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2006;3:CD005112.

47. Reinisch W et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut. 2011;60:780–7.

48. Gies N et al. Treatment of ulcerative colitis with adalimumab or infliximab:

long-term follow-up of a single-centre cohort. Aliment Pharmacol Ther. 2010;32:522–8.

49. Sandborn WJ et al. A placebo-controlled trial of cyclosporine enemas for mildly to moderaty active left-sided ulcerative colitis. Gastroenterology. 1994;106:1429-35.

50. Lawrance IC, Copeland TS. Rectal tacrolimus in the treatment of resistant ulcerative proctitis. Aliment Pharmacol Ther. 2008;28(10):1214-20.

51. van Dieren JM et al. Local application of tacrolimus in distal colitis: feasible and safe. Inflamm Bowel Dis. 2009;15(2):193-8.

52. Bouguen G et al. Infliximab for refractory ulcerative proctitis. Aliment Pharmacol Ther. 2010;31(11):1178-85.

53. Tanaka H et al. Short- and long-term outcomes of infliximab treatment for refractory ulcerative colitis and related prognostic factors: A Japanese single-center study. Inflammatory Bowel Dis. 2012;18:S36.

54. Motoya S et al. Efficacy of infliximab for refractory ulcerative colitis. J Gastroenterol Hepatol. 2012;27 S5:161-2.

55. Vivekanandarajah S et al. Role of infliximab as rescue therapy in hospitalised patients with severe, steroid refractory ulcerative colitis. Local experience. Liverpool and Bankstown hospitals, South Western Sydney Local Health District. Australia. J Crohns Colitis. 2012;6 S1: S141-2.

56. Palaniappan S et al. Mycophenolate mofetil therapy for refractory inflammatory bowel disease. Inflamm Bowel Dis. 2007;13(12):1488-92.

57. Fellermann K et al. Mycophenolate mofetil: lack of efficacy in chronic active inflammatory bowel disease. Aliment Pharmacol Ther. 2000;14(2):171-6.

58. Tan T, Lawrance IC. Use of mycophenolate mofetil in inflammatory bowel disease. World J Gastroenterol. 2009;15(13):1594-9.

59. Orth T et al. Mycophenolate mofetil versus azathioprine in patients with chronic active ulcerative colitis: a 12-month pilot study. Am J Gastroenterol. 2000;95(5):1201-7.

60. Oren R et al. Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter trial. Gastroenterology. 1996;110(5):1416-21.

61. Mañosa M et al. Methotrexate in ulcerative colitis: a Spanish multicentric study on clinical use and efficacy. J Crohns Colitis. 2011;5(5):397-401.

62. Nathan DM et al. A single center experience of methotrexate in the treatment of Crohn's disease and ulcerative colitis: a case for subcutaneous administration. J Gastroenterol Hepatol. 2008;23(6):954-8.

63. Cummings JR et al. Oral methotrexate in ulcerative colitis. Aliment Pharmacol Ther. 2005;21(4):385-9.

64. Carbonnel F. Methotrexate: a drug of the future in ulcerative colitis? Curr Drug Targets. 2011;12:1413–6.

65. Herfarth HH et al. Efficacy of methotrexate in ulcerative colitis: failure or promise. Inflamm Bowel Dis. 2010;16:1421–30.

66. Stange EF. Extended abstract: Tacrolimus and cyclosporine in inflammatory bowel disease. Dig Dis. 2012;30 Suppl 3:119-20.

67. Schmidt KJ et al. Short-term efficacy of tacrolimus in steroid-refractory ulcerative colitis - experience in 130 patients. Aliment Pharmacol Ther. 2013;37(1):129-36.

68. Baumgart DC et al. Tacrolimus is safe and effective in patients with severe steroid-refractory or steroid-dependent inflammatory bowel disease--a long-term follow-up. Am J Gastroenterol. 2006;101(5):1048-56.

69. Baumgart DC et al. Rescue therapy with tacrolimus is effective in patients with severe and refractory inflammatory bowel disease. Aliment Pharmacol Ther. 2003;17(10):1273-81.

70. Fellermann K et al. Tacrolimus: a new immunosuppressant for steroid refractory inflammatory bowel disease. Transplant Proc. 2001;33(3):2247-8.

71. Fellermann K et al. Steroid-unresponsive acute attacks of inflammatory bowel disease: immunomodulation by tacrolimus (FK506). Am J Gastroenterol. 1998;93:1860–6.

72. Högenauer C et al. Effect of oral tacrolimus (FK 506) on steroid-refractory moderate/severe ulcerative colitis. Aliment Pharmacol Ther. 2003;18(4):415-23.

73. Watanabe O et al. Short- and long-term efficacy of tacrolimus in patients with refractory ulcerative colitis. Digestive Disease Week. Abstract Su1241. 18-21 May, 2013, Orlando, Florida, USA.

74. Bonaz B, Boitard J, Marteau P et al. Tioguanine in patients with Crohn's disease intolerant or resistant to azathioprine/mercaptopurine. Aliment Pharmacol Ther 2003;18:401–408.

75. Teml A et al. A prospective, open-label trial of 6-thioguanine in patients with ulcerative or indeterminate colitis. Scand J Gastroenterol. 2005;40(10):1205-13.

76. van Asseldonk DP et al. Prolonged thioguanine therapy is well tolerated and safe in the treatment of ulcerative colitis. Dig Liver Dis. 2011;43(2):110-5.

77. Moreau AC et al. Association between thiopurines metabolites levels and clinical remission in IBD patients: An updated meta-analysis. Gastroenterology. 2013;144:S250-1.

78. Tibble JA et al. Surrogate markers of intestinal inflammation are predictive of relapse in patients with inflammatory bowel disease. Gastroenterology. 2000;119(1):15-22.

79. Van Rheenen PF et al. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis. BMJ. 2010;341:c3369.

80. Creed TJ et al. Basiliximab (anti-CD25) in combination with steroids may be an effective new treatment for steroid-resistant ulcerative colitis. Aliment Pharmacol Ther. 2003;18:65-75.

81. Creed TJ et al. Basiliximab for the treatment of steroid-resistant ulcerative colitis: further experience in moderate and severe disease. Aliment Pharmacol Ther. 2006;23;1435-42.

82. Van Assche G et al. A pilot study on the use of the humanized anti-interleukin-2 receptor antibody daclizumab in active ulcerative colitis. Am J Gastroenterol. 2003;98:369–76.

83. Plevy S et al. A phase I study of visilizumab, a humanized anti-CD3 monoclonal antibody, in severe steroid-refractory ulcerative colitis. Gastroenterology. 2007;133(5):1414-22.

84. Baumgart DC et al. Prospective randomized open-label multicenter phase I/II dose escalation trial of visilizumab (HuM291) in severe steroid-refractory ulcerative colitis. Inflamm Bowel Dis. 2010;16(4):620-9.

85. Sands BE et al. Basiliximab does not increase efficacy of corticosteroids in patients with steroid-refractory ulcerative colitis. Gastroenterology. 2012;143:356-64.

86. Van Assche G et al. Daclizumab, a humanised monoclonal antibody to the interleukin 2 receptor (CD25), for the treatment of moderately to severely active ulcerative colitis: a randomised, double blind, placebo controlled, dose ranging trial. Gut. 2006;55(11):1568-74.

87. Sandborn WJ et al. Anti-CD3 antibody visilizumab is not effective in patients with intravenous corticosteroid-refractory ulcerative colitis. Gut. 2010;59(11):1485-92.

88. Sandborn WJ et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2013;doi:10.1053/j.gastro.2013.06.010. [Epub ahead of print].

89. Feagan BG et al. Treatment of ulcerative colitis with a humanized antibody to the alpha4beta7 integrin. N Engl J Med. 2005;352(24):2499-507.

90. Parikh A et al. Vedolizumab for the treatment of active ulcerative colitis: a randomized controlled phase 2 dose-

ranging study. Inflamm Bowel Dis. 2012;18(8):1470-9.

91. Parikh A et al. Long-term clinical experience with vedolizumab in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2013;19(8):1691-9.

92. Feagan BG et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369:699-710.

93. Sandborn WJ et al. Tofacitinib, an oral janus kinase inhibitor, in active ulcerative colitis. N Engl J Med. 2012;367:616-24.

NON-SURGICAL THERAPY FOR UNRESECTABLE HILAR CHOLANGIOCARCINOMA

Manuel Liberato,[1] Jorge Canena[2]

1. *Director of University Gastroenterology Centre-Nova Medical School, Hospital Cuf Infante Santo, Lisbon, Portugal*
2. *Professor and Chairman of Gastroenterology, Faculty of Medical Sciences and Gastroenterology Consultant, University Gastroenterology Centre – Nova Medical School, Lisbon, Portugal*

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ABSTRACT

Hilar cholangiocarcinoma (HCCA) is characterised by late clinical symptoms. As a consequence, most patients will not undergo surgery, and palliation is the main goal of therapy. For the few patients that undergo potentially curative surgery, the need for preoperative biliary drainage (PBD) continues to be debated and remains controversial, as there are many reports with conflicting results. For the palliation of unresectable HCCA, endoscopic or percutaneous transhepatic drainage (PTD) is typically preferred over surgical palliative resection. PTD can be useful in patients with altered anatomy, as a guide to endoscopic procedures (rendezvous technique), after failure of endotherapy or as a rescue therapy for the drainage of segments that have been opacified by endoscopy. Endoscopic palliative bile duct drainage can be performed with plastic stents (PSs) or self-expandable metal stents (SEMSs). Several studies have compared PSs and SEMSs for the palliation of HCCA, and all have been in favour of SEMS placement, which is associated with a lower number of reinterventions, superior cumulative stent patency and even improved survival. The optimal technique for endoscopic palliative metal stent placement and the benefits of bilateral versus unilateral stenting remain controversial and highly debated. Drainage of only 25-30% of the liver volume may be sufficient to ameliorate jaundice in most cases of HCCA. However, reports of bilateral drainage are associated with longer stent patency, lower reintervention rates and, perhaps, a better quality of life for patients. Furthermore, newly available stents may be associated with higher rates of technical success and increasing successful reintervention rates in bilateral stenting.

Keywords: Cholangiocarcinoma, endotherapy, metal stents, plastic stents.

INTRODUCTION

Cholangiocarcinoma (CCA) is a primary cancer of the bile ducts and it arises from the malignant transformation of cholangiocytes - the epithelial cells that line the biliary tract. CCA is the second most common primary hepatobiliary cancer after hepatocellular carcinoma, and it accounts for 3% of all gastrointestinal cancers worldwide.[1] More than 90% of CCAs are adenocarcinomas.[2] According to its location in the biliary tree, CCA may be classified into extrahepatic and intrahepatic types. The extrahepatic type is further divided into hilar (HCCA), middle and distal tumours.[3] The most common location of CCA is the main confluence of the hepatic ducts, which accounts for 60-70% of all CCAs.[4] First described by Altemeier et al.[5] in 1957, HCCA was only recognised as a distinct clinical entity in 1965 when Klatskin[6] reported a series of 13 patients. Now known as Klatskin tumours, HCCA has a reported annual incidence of 1.2 per 100,000 individuals in the United States, with males being the most affected.[1,3,4] The incidence of HCCA varies across the world, and it has been reported to be highest in the Khon Kaen province in the northeast region of Thailand, probably because of the high prevalence of liver fluke infestations.[3,7]

Table 1. The Bismuth-Corlette classification for malignant hilar stenosis.

Type	Lesion
I	Stricture is located in the proximal common hepatic duct and spares the confluence of hepatic ducts.
II	Stricture includes the confluence and spares the segmental hepatic ducts.
IIIa	Stricture reaches the right hepatic duct.
IIIb	Stricture reaches the left hepatic duct.
IV	Stricture is multicentric or involves the right and left hepatic ducts.

HCCA has an extremely poor prognosis, with a 5-year survival rate of <10%, and most patients are in their sixth or seventh decade of life.[1,3,4,8] Bismuth and Corlette[9] classified malignant hilar stenosis into four categories[9,10] according to the type of involvement of the hepatic ducts (Table 1). Although this classification does not characterise other structures such as the portal vein or the hepatic artery (which may help to predict surgical resectability), it is helpful when planning surgical resection or for endoscopic stent placement.[1,8]

Unfortunately, HCCA is characterised by late clinical symptoms such as jaundice, pruritus, malaise, and weight loss. As a consequence, patients with Klatskin tumours typically present at an advanced stage of disease and/or have associated significant comorbidities that make them poor candidates for potential curative surgery. Overall, only 10-20% of patients with HCCA will undergo complete surgical resection with tumour-free margins, which is associated with the best prognosis and the best long-term survival.[1,4,8] The need for preoperative biliary drainage (PBD) continues to be debated and remains controversial.[11-17] Some reports have suggested that PBD offers no advantage in decreasing perioperative mortality and morbidity.[11-13,15] Furthermore, PBD has been associated with an increased risk of infectious complications, prolonged hospital stays, and increased costs. Finally, there is an increased incidence of tumour seeding through the biliary system that is associated with percutaneous drainage and can lead to poor surgical outcomes.[15] A recent systematic review concluded that PBD had no clinical benefit in jaundiced patients with HCCA who were planned for surgery.[13] However, PBD is the established therapy in most centres with the rationale that PBD reverses cholestasis-associated hepatic and systemic toxicity as well as impaired hepatic regeneration.[17] A recent multicentre European study of PBD for HCCA evaluated 366 patients, and PBD was performed in 180 patients. The authors concluded that PBD did not affect overall postoperative mortality, but it was associated with a decreased mortality rate after right hepatectomy and an increased mortality rate after left hepatectomy. A preoperative serum bilirubin level >50 μmol/L was also associated with increased mortality, but only after right hepatectomy.[17] Furthermore, Japanese surgeons consider PBD to be mandatory in patients undergoing major hepatectomy.[14] A recent paper compared endoscopic stenting, endoscopic nasobiliary drainage and percutaneous drainage for PBD, and the authors concluded that endoscopic nasobiliary drainage was the most suitable method for initial PBD in patients with HCCA.[16]

For patients who will not undergo surgery, palliation is the main goal of therapy. The relief of biliary obstruction not only reduces jaundice and associated pruritus but also improves related symptoms such as anorexia and disturbed sleep patterns and leads to an improved quality of life. For palliation of unresectable HCCA, endoscopic or percutaneous transhepatic drainage (PTD) is typically preferred over surgical palliative resection. Surgical procedures are associated with increased morbidity, and no survival benefits have been demonstrated in patients submitted to palliative surgery.[1,2,4,8]

PERCUTANEOUS TRANSHEPATIC DRAINAGE VERSUS ENDOTHERAPY

Before any intervention for malignant hilar decompression, magnetic resonance cholangiopancreatography (MRCP) is strongly recommended to delineate the anatomy and plan the strategy for drainage.[1,2,4,8] PTD is more invasive than the endoscopic approach and is associated with several disadvantages: haemorrhage during liver puncture, the need for the placement of external biliary catheters before internal drainage with stent insertion is attempted, longer hospitalisation, patient discomfort and inflammation, and pain at the puncture site.[1] However, PTD can be useful in altered anatomy or as a guide to endoscopic procedures (in a rendezvous manoeuvre). Furthermore, PTD is indicated when MRCP reveals that endotherapy is not likely to be successful in patients with Bismuth III or IV complex strictures.[4] A recent retrospective study comparing endoscopy versus PTD with internal drainage with metal stents after external drainage in patients with Bismuth type III or IV HCCA demonstrated a higher initial success rate and a low level of procedure-related cholangitis in favour of the PTD approach.[18] Finally, PTD can be used after failure of endotherapy or as a rescue therapy for the drainage of segments that have been opacified by endoscopy and were not decompressed, as this is associated with poor outcomes. Endoscopic drainage should be recommended as the first-line drainage technique for malignant HCCA;[1,4,8] however, the final decision about the method of drainage should be considered along with anatomical factors, MRCP results, and local expertise with both methods.

ENDOTHERAPY

Plastic Stents Versus Self-Expandable Metal Stents

Endoscopic palliative bile duct drainage was first reported by Soehendra et al.[19] Currently, two types of endoscopic stents are available. With the introduction of duodenoscopes with 4.2 mm working channels in 1982, the endoscopic insertion of large-bore plastic biliary stents (PSs) became possible.[20] The main disadvantage of plastic endoprostheses is the relatively high occlusion rate caused by biliary sludge, which occurs at a median interval of 3 to 4 months after placement.[21] First described in 1989,[22,23] self-expandable metal stents (SEMSs) are available with different lengths, diameters, and delivery devices. SEMSs with a maximum diameter of 10

Table 2. Studies comparing the placement of plastic stents versus metal stents for palliation of hilar cholangiocarcinoma.

Author	Study design	Patients (n)	Main outcomes
Wagner et al.[28] 1993	RCT	Plastic (n=9) Metal (n=11)	Significantly long-term patency technical success rates, lower reintervention rates and diminished costs for SEMS group.
Sangchan et al.[7] 2012	RCT	Plastic (n=54) Metal (n=54)	Significantly longer patency, successful drainage and longer survival for SEMS group.
Mukai et al.[29] 2013	RCT	Plastic (n=30) Metal (n=30)	Significantly longer patency, lower costs and lower number of reinterventions for SEMS group. No survival benefit.
Liberato and Canena.[27] 2012	Retrospective	Plastic (n=231) Metal (n=249)	Significantly higher technical and clinical success rates in the intention-to-treat analysis, lower reintervention rates and longer patency for SEMS group in all Bismuth classifications. No survival benefit.
Perdue et al.[26] 2008	Prospective (30-day outcomes)	Plastic (n=28) Metal (n=34)	Significantly higher number of adverse outcomes including cholangitis, stent occlusion, migration, perforation, and/or the need for unplanned ERCP or PTD in plastic group.
Raju et al.[24] 2011	Retrospective	Plastic (n=52) Metal (n=48)	Significantly longer patency and lower number of reinterventions for SEMS group. No survival benefit.

RCT: randomised controlled trial; SEMS: self-expandable metal stent; PTD: percutaneous transhepatic drainage; ERCP: endoscopic retrograde cholangiopancreatography.

mm theoretically offer the optimal conditions for long-term drainage; in addition to having a larger diameter, SEMSs also have a fenestrated mesh that permits drainage from secondary branch ducts. PSs and SEMSs placed in HCCA have been associated with a lower duration of patency when compared to the median patency of PSs and SEMSs in the palliation of malignant distal obstruction.[21,24,25]

Several studies have compared PSs and SEMSs for the palliation of HCCA, and all have been in favour of SEMS placement (Table 2).[7,24,26-29] Three randomised controlled trials have compared PSs with SEMSs for unresectable HCCA drainage.[7,28-29] In an older study, 20 patients with type II-IV hilar malignancies were randomly assigned to receive PSs or SEMSs, which were placed using a combined endoscopic-percutaneous technique.[28] Although the sample size was small and most of the stents were placed by the percutaneous route, the authors observed higher long-term patency with a decreased incidence of cholangitis, higher technical success rates, significantly lower reintervention rates for stent failure, and diminished costs with reduced hospital stay for patients who received SEMSs. In another study from the Khon Kaen province, 108 patients were randomly allocated to receive SEMS or PS placement.[7] The authors reported that endoscopic biliary drainage with SEMSs was associated with a significantly increased successful drainage rate and longer survival compared with PS placement. In another study from Japan, 60 patients were enrolled and prospectively randomised into the PS or SEMS group.[29] SEMSs were significantly associated with longer patency, lower reintervention rates and lower overall treatment costs. No survival benefit was found in this trial.

In a recent study,[27] 480 patients with inoperable HCCA were retrospectively reviewed. Patients were divided into three groups according to the Bismuth classification and underwent PS or SEMS placement. The authors concluded that SEMS insertion for the palliation of hilar cholangiocarcinoma offered higher technical and clinical success rates in the intention-to-treat (ITT) analysis as well as lower reintervention rates and superior cumulative stent patency when compared with PS placement in all Bismuth classifications. Again, no survival benefit was found.

Endoscopic palliation of HCCA with SEMSs should be considered the gold standard of care, as it is associated with a lower number of reinterventions, superior cumulative stent patency and even improved survival.[1,4,7,8,24-29] Furthermore, the lower number of reinterventions, days of hospitalisation and hospital re-admissions observed for patients submitted to SEMS placement indicate a clear benefit for SEMSs, which can be translated into improved patient quality of life. A recent systematic review of the literature comparing PSs versus SEMSs concluded that the use of metal stents was associated with a significantly higher successful drainage rate, a lower early complication rate, longer stent patency, and longer patient survival.[30] PSs should be reserved for patients with a very low expected survival (1-2 months), for PBD (when it is considered and depending on the centre and country, as previously discussed in this article), and whether the patient is receiving photodynamic therapy because PSs should be removed during this treatment.[31-35] However, delivery of photodynamic therapy (PDT) is possible with an inserted SEMS as long as the dose is reduced.[35] PDT for palliation of HCCA has been shown to prolong survival in two randomised trials that included patients treated with PSs[32,33] and also in a non-randomised controlled study that included patients submitted to palliation with SEMSs.[34]

Unilateral Versus Bilateral Endoscopic Biliary Stenting

The optimal technique for endoscopic palliative metal placement and the benefits of bilateral versus unilateral stenting remain controversial and highly debated. De Palma et al.[36] reported the only prospective, randomised, controlled study comparing unilateral and bilateral drainage using PSs in 157 patients. In the ITT analysis, unilateral placement resulted in a significantly higher rate of stent insertion (88.6% versus 76.9%) and a lower rate of complications and early cholangitis when compared with bilateral placement. The authors concluded that the routine insertion of more than one stent would not be justified and that single stent insertion avoids the risk of further procedure-related complications and mortality. However, these results need to be interpreted with caution because of some study biases. Information about stent patency and occlusion rates in both groups

was not available. Furthermore, patient subgroup analyses were not performed, and there was a high number of patients with Bismuth type I stricture included, for which the placement of one stent is sufficient; thus, it is impossible to determine how the results might have been affected by their inclusion.

Bilateral drainage is, theoretically, more physiological than unilateral drainage,[8,37] although this may be disputed by reports suggesting that drainage of a mere 25-30% of the liver volume may be sufficient to ameliorate jaundice[37,38] in most cases of HCCA. Indeed, bilateral drainage may not be necessary in some cases, particularly if previous MRCP is used to select the optimal lobe and biliary segment(s) to be drained.[39,40] However, to preserve functional liver volume, unilateral drainage may be less effective than bilateral drainage. Furthermore, a report that assessed the relative volumetry of the liver on CT scans suggested that drainage of more than 50% of the liver volume is associated with prolonged survival.[41] Bilateral stenting has been reported to be more technically demanding.[42,43] Various techniques have been described for bilateral SEMS placement.[42-50] The most commonly used technique is the stent-in-stent (SIS) method (Figure 1),

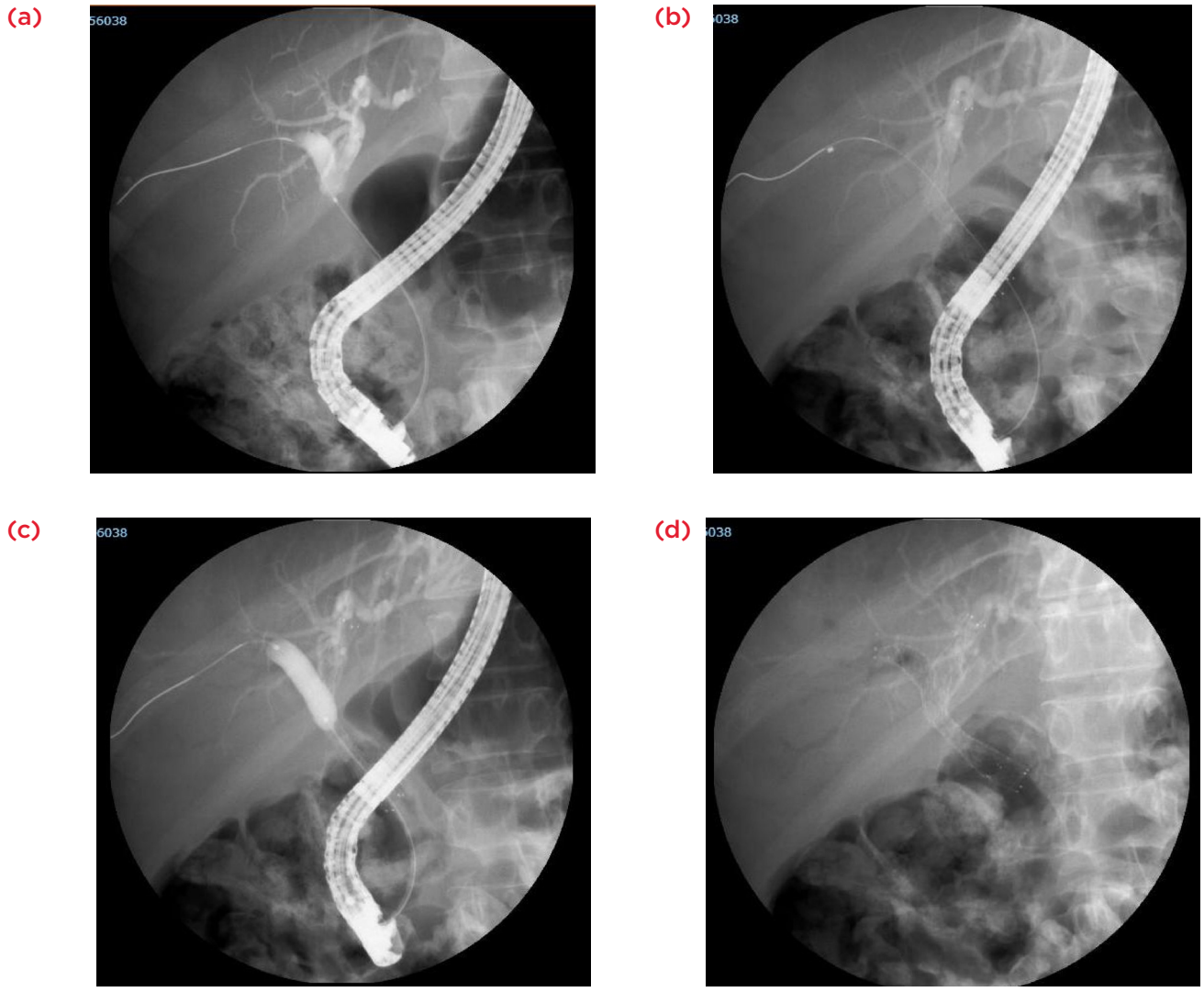

Figure 1. The stent-in-stent (SIS) method for bilateral SEMS placement.
(a) Cholangiogram of a malignant hilar stenosis (Bismuth II).
(b) After placement of the first SEMS in the left hepatic duct the guidewire was inserted, under fluoroscopic guidance, into the contralateral hepatic duct through the interstices of the initial SEMS.
(c) Balloon dilatation of the mesh interstices of the SEMS placed in the left hepatic duct to facilitate the passage of the second SEMS to the right hepatic duct.
(d) Fluoroscopic view of bilateral stenting to form a Y-shaped configuration.

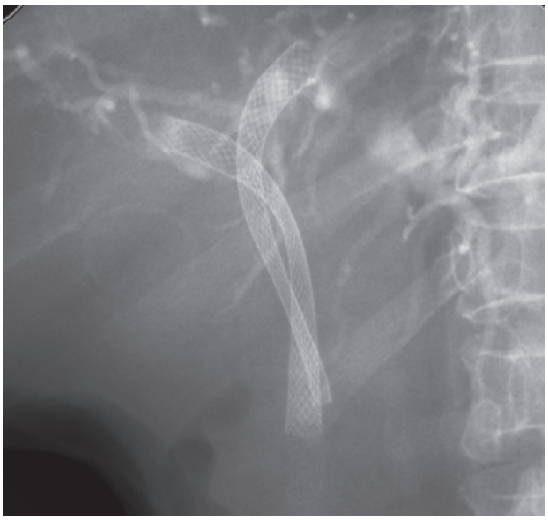

Figure 2. Bilateral stenting in a side by side configuration.
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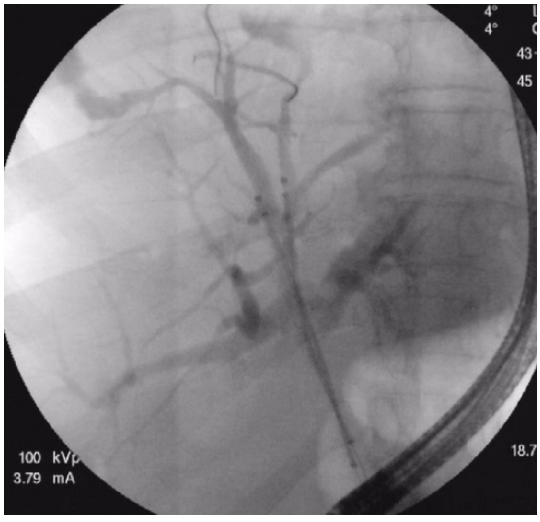
in which a wide-mesh SEMS (although a stent with a closed-cell configuration can also be used) is inserted into one side of the hepatic duct, and a second SEMS is positioned on the contralateral side across the mesh.[45,46] Recently, SEMSs with extra-wide open-mesh designs in the central portion to facilitate bilateral placement have been described, with encouraging results.[47,50,51] Other studies have described techniques to place an SEMS in a side by side (SBS) configuration (Figure 2),[27] with good results.[42-44] Recently, a novel SEMS was developed with a 6-French delivery system to allow the SBS insertion of bilateral SEMSs[49,52] (Figure 3).[27] No randomised trials comparing unilateral versus bilateral SEMS deployment are available. However, several reports have compared the deployment of one or the bilateral placement of SEMSs in unresectable HCCA[27,29,44,53] (Table 3). A recent retrospective review of 46 patients with hilar malignant obstruction compared unilateral (n=17) with bilateral (n=29) SEMS stenting.[44] Cumulative stent patency was significantly increased with bilateral stenting (median patency of 488 days versus 210 days, p=0.009), particularly in cases of CCA. Moreover, there were no significant differences between the two groups in terms of successful stent insertion, successful drainage or early or late complications. In a retrospective review, the outcomes of the unilateral (n=35) or bilateral (n=42) placement of SEMSs in patients with type II HCCA were analysed.[27] Bilateral stenting was associated with significantly fewer reinterventions and increased median stent patency. Again, technical success and clinical success were similar in the two groups.

One important issue is the determination of the technique that is better or associated with a lower complication rate. SBS deployment has been reported to occasionally cause portal vein occlusion and increase the rate of cholangitis due to the excessive expansion of the bile duct by parallel stents.

(a)



(b)

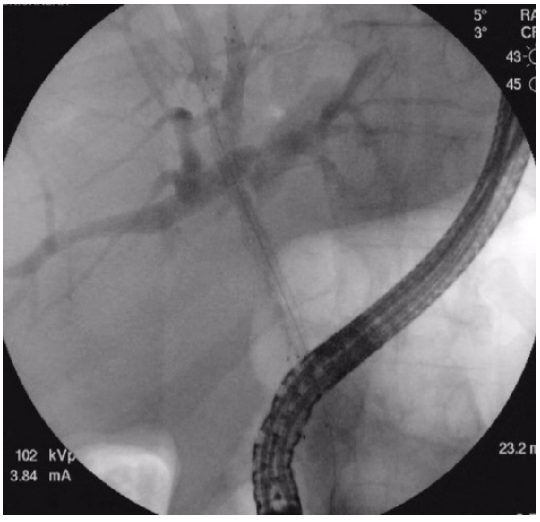


Figure 3. Bilateral stenting using a 6-French delivery system.
Reproduced with permission[27]
(a) Fluoroscopic view of side by side delivery systems pre-deployment.
(b) Fluoroscopic view of post-deployment bilateral stenting.

Table 3. Studies comparing unilateral placement versus bilateral placement of metal stents for palliation of hilar cholangiocarcinoma.

Author	Study design	Patients (n)	Main outcomes
Naitoh et al.[44] 2009	Retrospective	Uni (n=17) Bi (n=29)	Significantly cumulative stent patency in Bil group. Similar stent insertion, successful drainage and survival in two groups/Bil.
Iwano et al.[53] 2011	Retrospective	Uni (n=65) Bil (n=17)	Similar median stent patency, complication-free survival and survival in two groups. Significantly higher incidence of liver abscess in Bil group/Uni.
Liberato and Canena.[27] 2012	Retrospective	Uni (n=35) Bil (n=42)	Significantly longer stent patency and lower number of reinterventions for Bil group. Similar stent insertion and survival in two groups /Bil.
Mukai et al.[29] 2013	Prospective	Uni (n=14) Bil (n=26)	Similar stent patency in two groups. Significantly higher success rate of reintervention in Uni group/Uni.

Uni: unilateral; Bil: bilateral.

However, a recent study[54] compared SBS versus SIS deployment in 52 consecutive patients with malignant hilar obstruction. The authors found no differences in technical success and functional success between groups. SBS deployment was associated with a higher rate of complications and significantly better stent patency in a Kaplan-Meyer analysis but not in a multivariate analysis. Overall, it is unclear whether one technique is better than the other, and further studies on this issue are warranted.

One other concern with bilateral SEMS deployment is reintervention for stent dysfunction, which has been reported to be much more challenging in bilateral stenting.[24,29] However, two recent studies have reported a high success rate for reintervention after bilateral SEMS placement. One study using cross-wired SEMSs reported a technical success of 83.3% for the revision of cases where the primary deployed bilateral SEMSs were occluded. Another study using SBS deployment reported a revision success rate of 92% after stent occlusion.[55]

Therefore, the placement of unilateral or bilateral SEMSs in HCCA remains controversial. Selected cases with previous imaging guidance (MRCP) may be better served with unilateral drainage. In unilateral stenting, contrast medium injection into the intrahepatic ducts without adequate drainage should be avoided, as this is associated with uncontrolled cholangitis and poor prognosis.[56] However, bilateral stenting is associated with longer stent patency, a lower reintervention rate and, perhaps, better patient quality of life. Furthermore, newly available stents may be associated with higher rates of technical success and increasing successful reintervention rates. Hopefully, future well-designed, large-scale, multicentre studies will bring further light to the question of which technique (bilateral or unilateral stenting) should be recommended for the treatment of unresectable HCCA.

CONCLUSION

In conclusion, the endoscopic palliation of unresectable HCCA should be the preferred technique and should be performed with SEMSs. PTD can be useful in patients with altered anatomy, after failure of endotherapy or as a rescue therapy for the drainage of segments that have been opacified by endoscopy. Unilateral or bilateral stenting remains controversial although there are increasing reports that bilateral drainage is associated with better outcomes than unilateral drainage in selected cases.

REFERENCES

1. Larghi A et al. Management of hilar biliary strictures. Am J Gastroenterol. 2008;103:458-73.

2. Singh P, Patel T. Advances in the diagnosis, evaluation and management of cholangiocarcinoma. Curr Opin Gastroenterol. 2006;22:294-9.

3. Lazaridis KN, Gores GJ. Cholangiocarcinoma. Gastroenterology. 2005;128:1655-67.

4. Gerges C et al. Expandable metal stents for malignant hilar biliary obstruction. Gastrointest Endosc Clin N Am. 2011;21:481-97.

5. Altemeier WA et al. Sclerosing carcinoma of the major intrahepatic bile ducts. AMA Arch Surg. 1957;75:450-60.

6. Klatskin G. Adenocarcinoma of the hepatic duct at its bifurcation within the porta hepatitis: an usual tumor with distinctive clinical and pathologic features. Am J Med. 1965;38:241-7.

7. Sangchan A et al. Efficacy of metal and plastic stents in unresectable complex hilar cholangiocarcinoma: a randomized controlled trial. Gastrointest Endosc. 2012;76:93-9.

8. Srinivasan I, Kahaleh M. Metal stents for hilar lesions. Gastrointest Endosc Clin N Am. 2012;22:555-65.

9. Bismuth H, Corlette MB. Intrahepatic cholangioenteric anastomosis in carcinoma of the hilus of the liver. Surg Gynecol Obstet. 1975;140:170-8.

10. Bismuth H et al. Resection or palliation: priority of surgery in the treatment of hilar cancer. World J Surg. 1988;12:39–47.

11. Hatfield AR et al. Preoperative external biliary drainage in obstructive jaundice. A prospective controlled clinical trial. Lancet. 1982;2:896–9.

12. Ferrero A et al. Preoperative biliary drainage increases infectious complications after hepatectomy for proximal bile duct tumor obstruction. World J Surg. 2009;33:318–25.

13. Liu F et al. Preoperative biliary drainage before resection for hilar cholangiocarcinoma: Whether or not? A systematic review. Dig Dis Sci. 2011;56:663–72.

14. Yasuda I et al. Unilateral versus bilateral endoscopic biliary stenting for malignant hilar biliary strictures. Dig Endosc. 2013;25 (Suppl. 2):81-5.

15. Takahashi Y et al. Percutaneous transhepatic biliary drainage catheter tract recurrence in cholangiocarcinoma. Br J Surg. 2010;97:1860–6.

16. Kawakami H et al. Endoscopic nasobiliary drainage is the most suitable preoperative biliary drainage method in the management of patients with hilar cholangiocarcinoma. J Gastroenterol. 2011;46:242–8.

17. Farges O et al. Multicentre European study of preoperative biliary drainage for hilar cholangiocarcinoma. Br J Surg. 2013;100:274-83.

18. Paik WH et al. Palliative treatment with self-expandable metallic stents in patients with advanced type III or IV hilar cholangiocarcinoma: a percutaneous versus endoscopic approach. Gastrointest Endosc. 2009;69:55–62.

19. Soehendra N, Reynders-Frederix V. Palliative bile duct drainage – A new endoscopic method of introducing a transpapillary drain. Endoscopy. 1980;12:8-11.

20. Huibregtse K, Tytgat GN. Palliative treatment of obstructive jaundice by transpapillary introduction of large bore bile duct endoprosthesis. Gut. 1982;23:371-5.

21. Cheng JL et al. Endoscopic palliation of patients with biliary obstruction caused by nonresectable hilar cholangiocarcinoma: efficacy of self-expandable metallic Wallstents. Gastrointest Endosc. 2002;56:33-9.

22. Huibregtse K et al. Endoscopic placement of expandable metal stents for biliary strictures-a preliminary report on experience with 33 patients. Endoscopy. 1989;21:280–2.

23. Neuhaus H et al. Self-expanding biliary stents: preliminary clinical experience. Endoscopy. 1989;21:225–8.

24. Raju RP et al. Optimum palliation of inoperable hilar cholangiocarcinoma: comparative assessment of the efficacy of plastic and self-expanding metal stents. Dig Dis Sci. 2011;56:1557-64.

25. Chang WH et al. Outcome in patients with bifurcation tumors who undergo unilateral versus bilateral hepatic duct drainage. Gastrointest Endosc. 1998;47:354–62.

26. Perdue DG et al. Plastic versus self-expanding metallic stents for malignant hilar biliary obstruction: a prospective multicenter observational cohort study. J Clin Gastroenterol. 2008;42:1040-6.

27. Liberato M, Canena J. Endoscopic stenting for hilar cholangiocarcinoma: efficacy of unilateral and bilateral placement of plastic and metal stents in a retrospective review of 480 patients. BMC Gastroenterol. 2012;12:103.

28. Wagner HJ et al. Plastic endoprostheses versus metal stents in the palliative treatment of malignant hilar biliary obstruction. A prospective and randomized trial. Endoscopy. 1993;25:213–18.

29. Mukai T et al. Metallic stents are more efficacious than plastic stents in unresectable malignant hilar biliary strictures: a randomized controlled trial. J Hepatobiliary Pancreat Sci. 2013;20:214-22.

30. Hong W et al. Endoscopic stenting for malignant hilar biliary obstruction: should it be metal or plastic and unilateral or bilateral? Eur J Gastroenterol Hepatol. 2013;25;1105-12.

31. Dumonceau JM et al. Biliary stenting: indications, choice of stents and results: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. Endoscopy. 2012;44:277-98.

32. Ortner MEJ et al. Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study. Gastroenterology. 2003;125:1355-63.

33. Zoepf T et al. Palliation of nonresectable bile duct cancer: improved survival after photodynamic therapy. Am J Gastroenterol. 2005;100:2426-30.

34. Gerhardt T et al. Combination of bilateral metal stenting and trans-stent photodynamic therapy for palliative treatment of hilar cholangiocarcinoma. Z Gastroenterol. 2010;48:28-32.

35. Wang L-W et al. Self-expandable metal stents and trans-stent light delivery: are metal stents and photodynamic therapy compatible? Lasers Surg Med. 2008;40:651-9.

36. De Palma GD et al. Unilateral versus bilateral endoscopic hepatic duct drainage in patients with malignant hilar biliary obstruction: results of a prospective, randomized, and controlled study. Gastrointest Endosc. 2001;53:547–53.

37. Kato H et al. Endoscopic bilateral deployment of multiple metallic stents for malignant hilar biliary strictures. Dig Endosc. 2013;25 (Suppl 2):75-80.

38. De Palma GD et al. Unilateral placement of metallic stents for malignant hilar obstruction: a prospective study. Gastrointest Endosc. 2003;58:50-3.

39. Hintze RE et al. Magnetic resonance cholangiopancreatography-guided unilateral endoscopic stent placement for Klatskin tumors. Gastrointest Endosc. 2001;53:40-6.

40. Freeman ML, Overby C. Selective MRCP and CT-targeted drainage of malignant hilar biliary obstruction with self-expanding metallic stents. Gastrointest Endosc. 2003;58:41-9.

41. Vienne A et al. Prediction of drainage effectiveness during endoscopic stenting

of malignant hilar strictures: the role of liver volume assessment. Gastrointest Endosc. 2010;72:728–35.

42. Hookey LC et al. Use of a temporary plastic stent to facilitate the placement of multiple self-expanding metal stents in malignant biliary hilar strictures. Gastrointest Endosc. 2005;62:605-9.

43. Dumas R et al. Endoscopic bilateral metal stent placement for malignant hilar stenoses: identification of optimal technique. Gastrointest Endosc. 2000;51:334-8.

44. Naitoh I et al. Unilateral versus bilateral endoscopic metal stenting for malignant hilar biliary obstruction. J Gastroenterol Hepatol. 2009;24:552-7.

45. Neuhaus H et al. The "stent through wire mesh technique" for complicated biliary strictures. Gastrointest Endosc. 1993;39:553-6.

46. Chahal P, Baron T. Expandable metal stents for endoscopic stent-within-stent placement for malignant hilar biliary obstruction. Gastrointest Endosc. 2010;71:195-9.

47. Kim JY et al. Usefulness of slimmer and open-cell-design stents for endoscopic bilateral stenting and endoscopic revision in patients with hilar cholangiocarcinoma (with video). Gastrointest Endosc. 2009;70:1109-15.

48. Park DH et al. Newly designed stent for endoscopic bilateral stent-in-stent placement of metallic stents in patients with malignant hilar biliary strictures: multicenter prospective feasibility study (with videos). Gastrointest Endosc. 2009;69:1357-60.

49. Chennat J, Waxman I. Initial performance profile of a new 6F self-expanding metal stent for palliation of malignant hilar biliary obstruction. Gastrointest Endosc. 2010;72:632-6.

50. Liberato M, Pontes J. "Tumores de las Vias Biliares y del Pancreas," Vázquez-Iglesias J, Aguirre P (eds.), In Endoscopia Digestiva Diagnóstica y Terapéutica (2008), Madrid: Editorial Medica Panamericana, pp. 551-72.

51. Lee TH et al. Primary and revision efficacy of cross-wired metallic stents for endoscopic bilateral stent-in-stent placement in malignant hilar biliary strictures. Endoscopy. 2013;45:106-13.

52. Law R, Baron TH. Bilateral metal stents for hilar biliary obstruction using a 6Fr delivery system: outcomes following bilateral and side-by-side stent deployment. Dig Dis Sci. 2013;58:2667-72.

53. Iwano H et al. Unilateral versus bilateral drainage using self-expandable metallic stent for unresectable hilar biliary obstruction. Dig Endosc. 2011;23:43–8.

54. Naitoh I et al. Side-by-side versus stent-in-stent deployment in bilateral endoscopic metal stenting for malignant hilar biliary obstruction. Dig Dis Sci. 2012;57:3279-85.

55. Lee TH et al. Technical feasibility and revision efficacy of the sequential deployment of endoscopic bilateral side-by-side metal stents for malignant hilar biliary strictures: a multicenter prospective study. Dig Dis Sci. 2013;58:547-55.

56. Chang WH et al. Outcome in patients with bifurcation tumors who undergo unilateral versus bilateral hepatic duct drainage. Gastrointest Endosc. 1998;47:354–62.

ENDOSCOPIC NECROSECTOMY AS TREATMENT FOR INFECTED PANCREATIC NECROSIS

Dr. Christian Jürgensen

Head of Endoscopy CCM, Department of Gastroenterology, Charité University, Berlin, Germany

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ABSTRACT

Necrotising pancreatitis can be life-threatening, but the introduction of endoscopic necrosectomy has led to a tremendous reduction of lethality. This review describes the technique and role of this method between conservative treatment and other interventional methods such as percutaneous drainage and surgery of superinfected necrosis. A little more than a decade after its introduction, endoscopic necrosectomy has become the gold standard in the interventional treatment of superinfected necrosis.

Keywords: Endoscopic necrosectomy, necrotising pancreatitis, interventional therapy, NOTES.

INFECTION IN NECROTISING PANCREATITIS

The Lethal Complication of the Second Phase

Acute pancreatitis is a common disease with a low morbidity in mild forms. However, severe acute pancreatitis can be life-threatening.[1] The lethality during the first 2 weeks is mostly due to consequences of (multi) organ failure.[2] This phase is dominated by the treatment of its different manifestations, such as acute respiratory distress syndrome (ARDS).

From the beginning of the third week, septic complications become dominant and are the main reason for lethality during the second phase of acute pancreatitis. Endoscopic necrosectomy, as well as other interventions, address these infectious problems. To know the onset of the pancreatitis can be helpful to distinguish these two phases, both being associated with signs of inflammation such as fever or leukocytosis.

Indication for Intervention and Timing

The treatment of the infected necrosis has shifted from aggressive and early surgery to a delayed and less invasive approach. Asymptomatic patients can usually be followed without any intervention. Conservative treatment has been shown to be successful in many patients, even for necrosis with proven infection.[3] However, the clinical course can force one to act. Like other treatment options, endoscopic necrosectomy is indicated only for those patients who suffer from symptoms such as sepsis, pain, or inability to take food orally. Procedures such as surgery, drainage, or endoscopic necrosectomy intend to control infection by drainage of pus, which is supplemented by removal of necroses. These necroses can be judged as fertile soil for bacteria and its extraction facilitates healing. The diagnosis of necrosis within a cavity is a challenge, but is of great impact for further treatment. Endoscopic ultrasound (EUS) can be helpful to diminish solid necrosis from fluid. As discussed above, infection is a problem not before the third week in the course of acute pancreatitis. Therefore, patients do not benefit from an earlier infection-driven therapeutic approach. This pathophysiological principle is supported by clinical data from surgical cohorts,[4] and likewise accepted for endoscopic necrosectomy.

ENDOSCOPIC NECROSECTOMY

Growing Acceptance

The initial description of endoscopic necrosectomy in 2000 by Seifert et al.[5] has been a milestone in the history of endoscopy technique. It is the first clinically established application of NOTES (natural orifice transluminal endoscopic surgery) and avoids much of the lethality related to superinfection in necrotising pancreatitis. It has passed the stages of a new method, from case report to small case series, multicentre studies[6-8] and a randomised study.[9]

The mentioned multicentre studies demonstrated a mortality of endoscopic necrosectomy of 6-8%, which is far less than reported for surgical cohorts (25-34%).[10-12] The minimal invasiveness, but also the option of early mobilisation, immediate enteral feeding, and the pain reduction by avoiding a transcutaneous approach, may contribute to its success. However, the mentioned randomised trial[9] was small (n=22) and addressed inflammatory markers, where a significant benefit for endoscopic necrosectomy was shown. The difference in lethality (n=4 for the surgical group versus n=1 for endoscopic necrosectomy) did not reach significance, since the study was underpowered to answer the superiorty of one or both approaches. Therefore, the question of superiority in terms of mortality is not answered definitively. In light of the above mentioned studies, a recruitment for a larger randomised study may have become impossible and even expert surgical centres have started to refer to endoscopic necrosectomy as first-step treatment. Major drawbacks are the limitation to specialised centres and the high demand on endoscopy time. Additionally, the method is associated with risks such as perforation, bleeding, and air embolism.

Technique

The endoscopic procedures constituting endoscopic necrosectomy can be assigned to three steps: access, necrosectomy and consolidation.[13]

The access to symptomatic pancreatic necrosis is the first step in the endoscopic treatment. The drainage of infected fluids results in a tremendous improvement in the patient's clinical situation. The location of the transluminal puncture has to be chosen carefully, since it defines the route for further interventions. The formerly blind procedure has become controlled to the millimetre since the introduction of endoscopic ultrasound, and interposing vessels can be circumvented (Figure 1). Additionally, non-bulging cavities or those with more than 10 mm distance to the gastrointestinal wall have become accessible.[14,15]

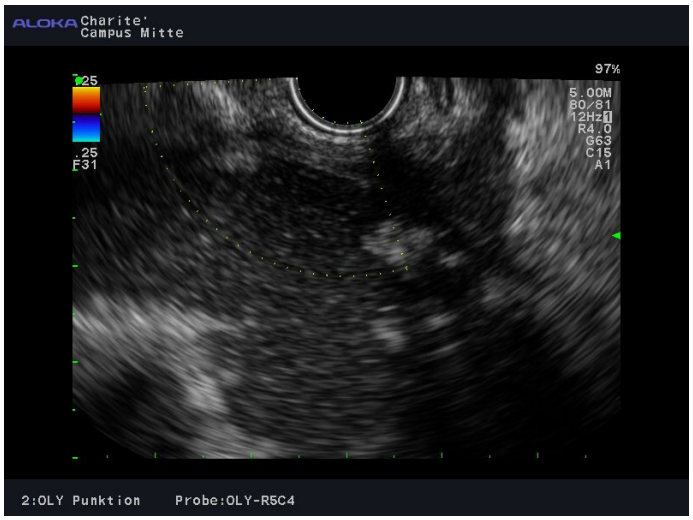

Figure 1. Endoscopic ultrasound from a gastral position before cyst drainage: colour Doppler mode is able to exclude intervening vessels.
The cavity is shown with echogenic fluid and echogenic solid structures (bottom left) corresponding with necrotic material. Note close contact of gastric wall and necrotic cavity.

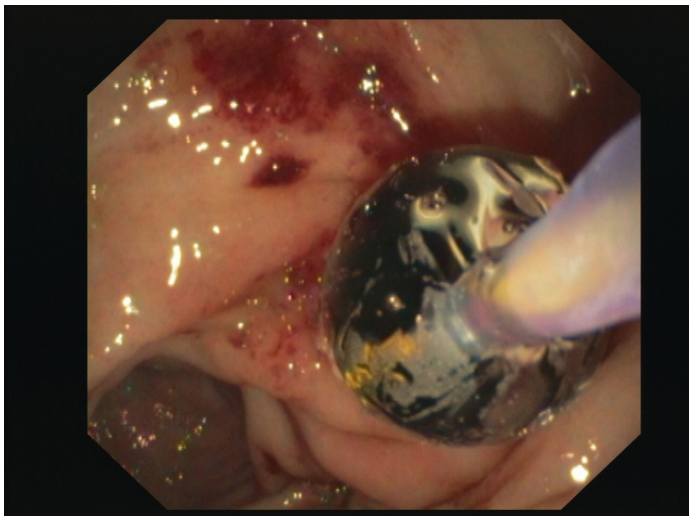

Figure 2. Endoscopic view from a gastric position: wire guided balloon dilation to broaden an access into the cavity at the gastric posterior wall.

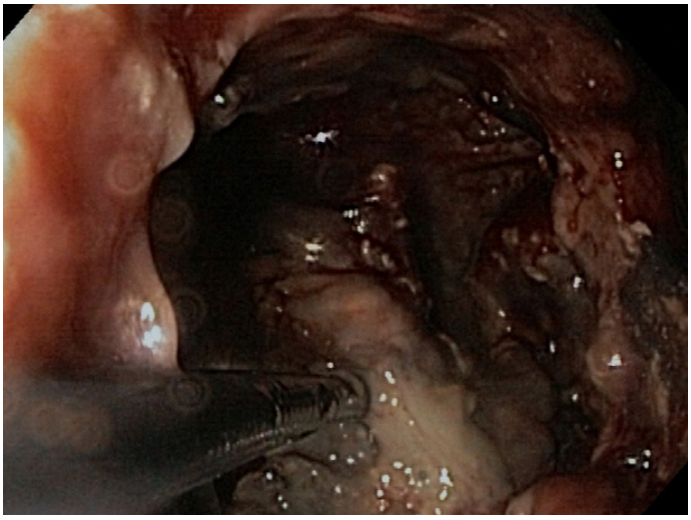

Figure 3. Internal endoscopic aspect of the cavity: removal of necrosis by use of a polyp grasper.

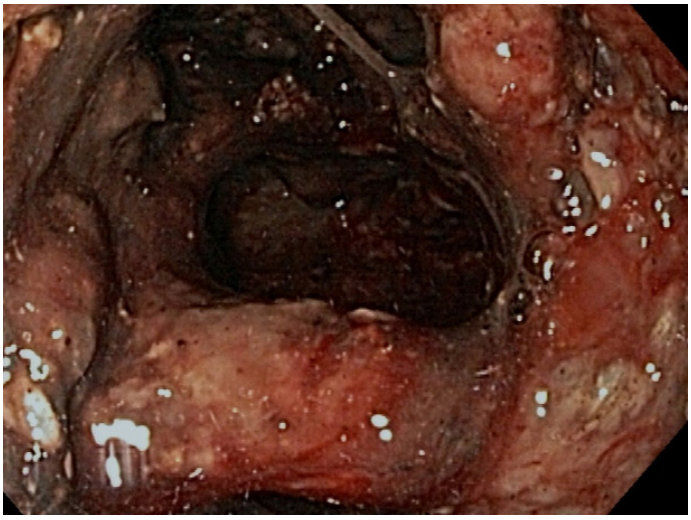

Figure 4. Internal endoscopic aspect of the cavity after removal of most of the necroses: vital splenic artery crossing the lumen.

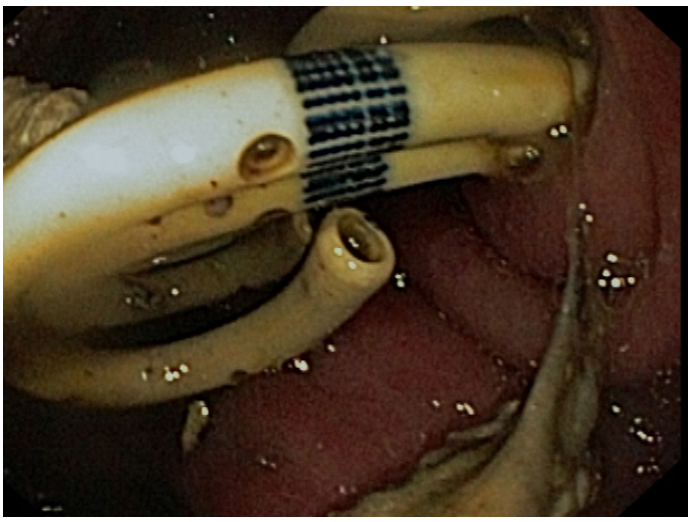

Figure 5. Endoscopic view of the gastric posterior wall: three double pigtail drainages left in place to keep the access open until a complete resolution of the cavity is achieved.

EUS-guided needle puncture is followed by the introduction of a guide wire under fluoroscopic co-control and dilation with a plethora of instruments (Soehendra-retriever, bougies, and dilation balloons, see Figure 2). The resulting channel is maintained by drainages or stents to offer time for subsequent consolidation before proceeding to necrosectomy. In most patients, a maximum diameter of 18 to 20 mm can be achieved during the first procedure. Broad access usually results in rapid general improvement and easier manoeuvring during the following interventions.

The necrosectomy itself may require many hours of endoscopy in order to remove the necrotic material with suboptimal instruments such as snares and polyp graspers still used today. The aim is to track the necrotic material into the stomach and to spare vital structures such as remaining pancreatic tissue or the splenic artery (Figure 3, 4). Sometimes the discrimination of these structures can be difficult but re-inspection during a follow-up session is helpful in most cases. In total, a number of three necrosectomy sessions each lasting roughly 2 hours may be required.

After removal of the necrotic material, the cavity is left with several transmural drains in place to ascertain the flow of remaining fluids during regression (Figure 5). The patient is sent home. After achieving remission of the cavity, 6 to 8 weeks later, the drains can be removed. The risk of persisting or recurrent infection becomes negligible by complete removal of the necrotic material.

ROLE OF SURGERY AND PERCUTANEOUS DRAINAGE

The role of surgery in the treatment of infected pancreatic necrosis has shifted from being the gold standard to a backup method. However, indications persist where surgical intervention may be needed, when:

- endoscopic necrosectomy as treatment modality is not available and transport to a specialised endoscopy centre is not feasible;
- no endoscopic access to symptomatic necrosis could be achieved;
- complications of endoscopic therapy such as perforation or sustained bleeding occured;

• cholecystectomy after biliary pancreatitis is necessary.

In return, endoscopic necrosectomy may be helpful in patients when remnant necrotic tissue becomes symptomatic after initial surgery.

Sole percutaneous drainage is feasable for infected pancreatic necrosis, but it is time consuming and may require large diameter drains. Today it can be a part of the treatment.[16] It may be combined with endoscopic necrosectomy in situations such as:

• initial stabilisation by percutaneous drainage resulting in decompression and regression of septic symptoms;

• additional access to flush from outside;

• drainage of remnant infected fluid collections not accessible by transluminal endoscopic approach.

It should be kept in mind that the endoscopic approach can be easier if the cavity is not 'emptied' by too long lasting initial external drainage. The otherwise resulting smaller size of the cavity and the more or less solid remnant necroses can hinder endoscopic manoeuvres within the cavity. Additionally, external drainage may increase the distance to the gastric wall and thereby hamper to achieve an endoscopic access.

CONCLUSION

Within a little more than a decade, endoscopic necrosectomy - if available - has become the method of choice for symptomatic pancreatic necrosis. The decision for endoscopic intervention has to be carefully balanced between conservative treatment and the requirement of additional and alternative options. The time consuming technique and the need of high level endoscopy are limiting this method to highly specialised referral endoscopy centres. The best treatment for patients with symptomatic necrosis depends on the locally available treatment options and the ability to transfer a patient to an expert endoscopic centre. As long as high level endoscopic necrosectomy is limited to these centres, the proclamation of a new gold standard has to be postponed.

REFERENCES

1. Pandol SJ et al. Acute pancreatitis: bench to the bedside. Gastroenterology. 2007;132:1127-51.

2. Carnovale A et al. Mortality in acute pancreatitis: is it an early or a late event? JOP. 2005;6:438-44.

3. Runzi M et al. Severe acute pancreatitis: nonsurgical treatment of infected necroses. Pancreas. 2005;30:195-9.

4. Hartwig W et al. Reduction in mortality with delayed surgical therapy of severe pancreatitis. J Gastrointest Surg. 2002;6:481-7.

5. Seifert H et al. Retroperitoneal endoscopic debridement for infected peripancreatic necrosis. Lancet. 2000;356:653-5.

6. Seifert H et al. Transluminal endoscopic necrosectomy after acute pancreatitis: a multicentre study with long-term follow-up (the GEPARD Study). Gut. 2009;58:1260-6.

7. Gardner TB et al. Direct endoscopic necrosectomy for the treatment of walled-off pancreatic necrosis: results from a multicenter U.S. series. Gastrointest Endosc. 2011;73:718-26.

8. Yasuda I et al. Japanese multicenter experience of endoscopic necrosectomy for infected walled-off pancreatic necrosis: The JENIPaN study. Endoscopy. 2013;45:627-34.

9. Bakker OJ et al. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. JAMA. 2012;307:1053-61.

10. Connor S et al. Early and late complications after pancreatic necrosectomy. Surgery. 2005;137:499-505.

11. Rau B et al. Surgical treatment of necrotizing pancreatitis by necrosectomy and closed lavage: changing patient characteristics and outcome in a 19-year, single-center series. Surgery. 2005;138: 28-39.

12. Besselink MG et al. Surgical intervention in patients with necrotizing pancreatitis. Br J Surg. 2006;93:593-9.

13. Jurgensen et al. Endoscopic ultrasound-guided endoscopic necrosectomy of the pancreas: is irrigation necessary? Surg Endosc. 2012;26:1359-63.

14. Varadarajulu S et al. Role of EUS in drainage of peripancreatic fluid collections not amenable for endoscopic transmural drainage. Gastrointest Endosc. 2007;66:1107-19.

15. Park DH et al. Endoscopic ultrasound-guided versus conventional transmural drainage for pancreatic pseudocysts: a prospective randomized trial. Endoscopy. 2009;41:842-8.

16. Ross A et al. Combined endoscopic and percutaneous drainage of organized pancreatic necrosis. Gastrointest Endosc. 2010;71:79-84.

THE VERSATILE ROLE OF THE VAGUS NERVE IN THE GASTROINTESTINAL TRACT

Nathalie Stakenborg, Martina Di Giovangiulio, Guy E. Boeckxstaens, Gianluca Matteoli

Department of Clinical and Experimental Medicine, Translational Research Center for Gastrointestinal Disorders (TARGID), University of Leuven, Leuven, Belgium

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ABSTRACT

The vagus nerve, the major nerve of the parasympathetic nervous system, innervates several organs from the neck to the abdomen. The vagal branches contain afferent (i.e. sensory) and efferent (i.e. motor) fibres contributing to a bidirectional communication between the visceral organs and the brain. The extensive vagal innervation of the body indicates that vagus nerve has a multitude of physiological functions. Specifically, the gastrointestinal (GI) tract is densely innervated by the vagus nerve and the latter plays a crucial role in GI functions such as food intake, digestion, and GI barrier function. In addition, the vagus nerve has immunomodulatory properties suggesting that activation of the parasympathetic innervation of the GI tract could act as a new therapeutic tool to treat intestinal immune diseases. This review summarises the anatomical and physiological properties of the vagal innervation of the GI tract.

Keywords: Parasympathetic nervous system, vagus nerve, gastrointestinal tract.

TOPOGRAPHICAL ANATOMY OF THE VAGUS NERVE

The vagus nerve, the main contributor of the parasympathetic nervous system, is the tenth cranial nerve originating from the medulla oblongata in the central nervous system. Within the medulla, the cell bodies of vagal preganglionic neurons are found in the nucleus ambiguous (NA) and the dorsal motor of the vagus (DMV). These nuclei supply fibres to the vagus nerve, which emerges from the cranium via the jugular foramen.[1] At the level of the jugular foramen, the superior jugular ganglion of the vagus provides cutaneous branches to the auriculus and external acoustic meatus.[2,3] Just distally, there is a second ganglion, referred to as the nodose ganglion, collecting sensory innervation from visceral organs. The cell bodies of afferent (i.e. sensory) neurons are located in the latter ganglion and project to the nucleus of the solitary tract (NTS). This nucleus relays input to the medulla in order to regulate the cardiovascular, respiratory and gastrointestinal (GI) functions.[4]

The cervical vagus descends within the carotid sheath alongside the carotid artery and internal jugular vein. Cardiac vagal branches leave the cervical vagus and join the cardiac plexus. The left and right recurrent laryngeal nerve, arising at the level of the aortic arch and subclavian artery respectively, also contribute to the cardiac innervation. Besides the heart, both vagi innervate the lungs through the pulmonary plexus.[1]

INNERVATION OF THE GI TRACT

More distally, the left and right vagus run with the oesophagus through the diaphragmatic hiatus. Upon entering the abdominal cavity, the left and right vagus become the anterior and posterior

vagus, respectively.[1,5,6] However, one has to keep in mind that each trunk receives fibres from both cervical vagus nerves.[5] The number of posterior and anterior trunks passing through the diaphragmatic opening is variable, up to two in the former and three in the latter.[5] The anterior trunk distributes gastric branches to the anterior aspect of the stomach and gives off a hepatic branch. Besides innervating the liver, the hepatic stem gives off branches to the pylorus and the proximal part of the duodenum and pancreas. On the other hand, the posterior trunk distributes one gastric branch to the proximal posterior aspect of the stomach and another to the coeliac plexus, which innervates the spleen and GI tract reaching as far as the left colonic flexure.[1,5,6] The large intestine receives additional parasympathetic innervation through the pelvic splanchnic nerve (S2-S4), which terminates in the pelvic plexus and emerges as the colonic and rectal nerve.[7-10]

The afferent vagus nerve innervates the GI tract via vagal terminals both in the lamina propria[11,12] and in the muscularis externa.[13-15] However, the efferent vagus nerve fibres only interact with neurons of the enteric nervous system (ENS). The ENS consists out of a dense meshwork of nerve fibres, situated in the submucosal (i.e. submucosal plexus) and external muscular compartment of the intestine (i.e. myenteric plexus).[16] By means of electrophysiological and anterograde tracer studies, it was demonstrated that preganglionic parasympathetic fibres (i.e. both vagal and sacral innervation) directly interact with multiple postganglionic myenteric neurons by formation of varicosities, whereas few vagal fibres communicate with submucosal neurons.[17-20] The preganglionic innervation of the GI tract displays a typical rostro-caudal gradient with the highest density of innervated myenteric neurons in the stomach and duodenum followed by a progressive reduction in the small intestine and colon.[17] The fact that gastric myenteric neurons are activated by vagal input was also demonstrated immunohistochemically with the detection of c-Fos and phosphorylated c-AMP response element binding protein (p-CREB), which are markers for neuronal activity.[21,22] As activation of neurons within one ganglion is initiated after the same latency period, Schemann et al.[20] suggest that the vagal input to the ENS is monosynaptic. However, this is not confirmed by other studies.[22] Currently, three distinct vagal afferent terminals have been described. The specific location of each terminal has correlations with its physiological function.

VAGAL REGULATION OF GI PHYSIOLOGY

Vagal fibres are projected throughout the GI tract and interact with the gut to regulate food intake, digestion, barrier keeping, and immunity. Food intake leads to satiety through the activation of several pathways: the release of various peptides from enteroendocrine cells (EEC), the direct action of certain nutrients (e.g. short fatty acids[23]) (Figure 1A), and mechanoreceptor stimulation due to gastric distension (Figure 1B).[24] Most afferent vagal endings in the mucosal lamina propria are thought to be chemoreceptors sensing the presence of hormones, peptides and nutrients released by epithelial and neuroendocrine cells.[23,25-27] In contrast, the terminal vagal structures in the external muscle layers and the myenteric plexus are considered to be mechanoreceptors detecting GI distension.[13,14] These sensory signals are relayed to the NTS, in which the afferent information is processed. Appropriate vagal efferent output is transmitted from the DMV.[12] The latter has a major metabolic and dietary function, since electrical stimulation of DMV leads to an increased secretion of gastric acid,[28,29] insulin[28,30] and glucagon.[28,31] Moreover, the secretion of gastric acid,[32] insulin,[32-38] glucagon,[35-37] and pancreatic polypeptide[39,40] is also elevated when the peripheral vagus nerve is stimulated (Figure 1). These responses are all abolished by vagotomy,[41] administration of atropine,[35,40,42] or hexamethonium.[31,40] Besides its dietary and metabolic functions, the vagus nerve also has effects on the intestinal barrier function through immune cells (i.e. mast cells[43]) and the activation of enteric glial cells via the ENS.

Dietary Intake and Metabolism Regulation

Chemical stimulation

The EECs respond to nutrient sensing in the lumen by the basolateral secretion of leptin in the stomach[44] and cholecystokinin (CCK) in the small intestine.[45] Tracer studies showed that EECs lie in close vicinity to mucosal vagal afferent terminals projecting from the nodose ganglia via the myenteric plexus.[11,46] The close anatomical position between vagal afferents and EECs enables CCK and leptin to act as paracrine factors, which activate CCK-A[26] and Ob-R receptors[25,27] expressed on afferent fibres, respectively.[11]

Electrophysiological studies have confirmed these anatomical observations, since CCK stimulates afferent nerve fibres[47] and nodose ganglion cell bodies[48] via the CCK-A receptor. Leptin has also been reported to act in synergism with CCK through CCK-A receptors and afferent vagal fibres.[27,49] This afferent signalling is further relayed to the NTS.[49-51] Synergistic vagal activation by CCK and leptin leads to inhibition of food intake.[49,52,53] In addition, CCK alone inhibits gastric emptying[54-56] and stimulates biliary and pancreatic secretion (Figure 1).[57-59]

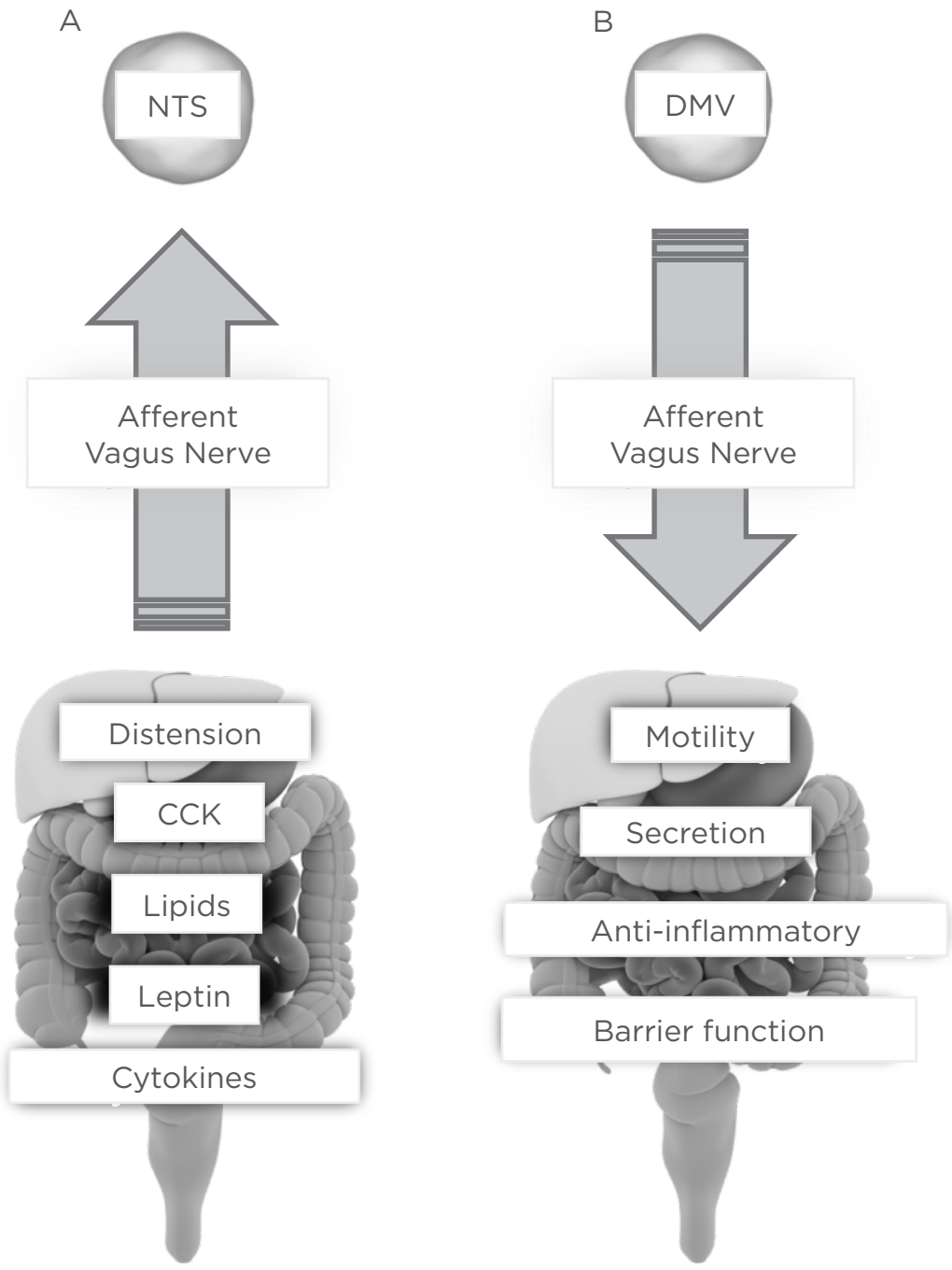

Figure 1. Vagal regulation of gastrointestinal (GI) physiology.
(A) Afferent vagal fibres receive information from the internal milieu of the GI tract via mechanical signalling and chemical (i.e. enteroendocrine hormone release and certain food nutrients) and immunological stimulation (i.e. proinflammatory cytokines).
(B) This sensory information is transmitted to the nucleus of the solitary tract (NTS) to mount an appropriate efferent (i.e. motor) response through the dorsal motor nucleus of the vagus (DMV), such as the secretion of neuroendocrine hormones and variations in GI motility, barrier function, and modulation of the intestinal immune response.

Indeed, the administration of specific CCK-A receptors antagonists (i.e. L364,718) prior to a meal increases food ingestion[54,60] and gastric emptying, but inhibits pancreatic secretion.[57,61,62] These effects of CCK are dependent on an intact vagal supply, since vagotomy[58,63,64] or destruction of small diameter vagal afferent C fibres by capsaicin abolish the actions of CCK.[54-56,58]

Mechanical stimulation

Besides chemosensory signal transduction, the afferent arch of the vagus is also activated by gastric distension through the stimulation of afferent vagal mechanoreceptor in the GI tract. Two candidate mechanoreceptors of the vagus nerve have been described: the intraganglionic laminar ending (IGLE)[13] and intramuscular arrays (IMAs).[14]

The former terminal consists of aggregates of terminal puncta associated with myenteric neurons as well as connective tissue structures surrounding the myenteric ganglia. IGLEs are the densest in the stomach and become sparse more caudally.[14,65-67] The close anatomical proximity between the connective tissue layers and the ganglia indicates that IGLEs are able to detect the shearing forces between the orthogonal muscle layers.[67,68] Electrophysiological studies confirm that IGLE could act as low threshold tension receptors, since distortion of the stomach leads to activation of tension-sensitive vagal mechanoreceptors.[46,67,69-71]

A second class of prominent vagal mechanoreceptors are IMAs, which consist of parallel arrays of neurite terminals coursing parallel to muscle bundles in the longitudinal or circular muscle layers[14,66,72] and lie in close vicinity of interstitial cells of Cajal (ICC).[15,73] IMAs are mostly located in the upper stomach, lower oesophageal and pyloric sphincters.[14,74-76] Based on the morphological features, IMAs appear to act as stretch receptors sensitive to shearing forces in the long axis. However, electrophysiological studies have not been able to unambiguously determine the true functionality of IMAs.[15,70,71]

The sensory vagal mechanoreceptors stimulated by gastric distension, are the first trigger of vago-vagal reflexes, such as gastric accommodation,[77] inhibition of food intake, and antral peristalsis (Figure 1).[78] Distension also appears to act in synergy with CCK to increase afferent activity and consequently decrease food intake.[79-83] However, Grundy et al.[84] disagree to the fact that CCK exerts a direct effect on vagal afferent mechanoreceptors, rather they suggest that the action of CCK is mediated through the sensory vagal chemoreceptors in the mucosa.[84]

The Vagus Nerve as Intestinal Barrier Keeper

Intestinal epithelial cells maintain a strict barrier between the external and internal environment via the expression of tight junctions. The tight junctions consist of a branching network of interacting transmembrane proteins, such as claudins and occludins. The loss of epithelial barrier integrity and thus tight junction expression enables bacterial translocation across the intestinal mucosa, which can initiate detrimental systemic inflammation after severe injuries.[85] Coimbra et al.[86-90] showed that there is increased intestinal permeability after haemorrhagic shock and traumatic brain and burn injuries, characterised by a decreased tight junction expression. Pharmacological, nutritional and electrical stimulation of the vagus nerve prevents the breakdown of the epithelial barrier via the stabilisation of tight junction expression (Figure 1).[88,89,91-96] Evidence suggests that VNS maintains the epithelial barrier integrity after severe injury by enteric glia activation. Several groups have demonstrated that the activation of glial cells leads to the release of S-nitrosoglutathione (GSNO), which increases the expression of tight junctions and improves mucosal integrity. These observations were confirmed *in vivo* by intraperitoneal (i.p.) injection of GNSO in inflammatory models.[97-100]

Vagus Nerve and Intestinal Immune System: The Cholinergic Anti-Inflammatory Pathway (CAIP)

For many decades, it has been acknowledged that a complex interplay exists between the nervous system and immune cells. The central nervous system (CNS) receives sensory information about the presence of inflammation and responds appropriately via two specific pathways: neuroendocrine and neural routes.[101]

Afferent arch of CAIP

In light of an overt infection, circular cytokines (i.e. IL-1 and TNF-α) or pathogenic components can be detected by higher brain structures (e.g.

circumventricular organs [CVO]) that are devoid of a blood brain barrier. Indeed, administration of intravenous (IV) endotoxin elicited c-Fos activation in the CVO and NTS.[102-104] These structures give direct input to motor neurons in the DMV, which project vagal efferents to the spleen. In this way, the vagus nerve is able to modulate the splenic immune response.[104-106]

The immune system does not only communicate with the brain via the circulation. In the case of more localised peripheral inflammation, in which the amount of proinflammatory cytokines is not detectable by the CVO, afferent vagal fibres and adjacent glomus cells are activated by cytokines/chemokines, such as IL-1 and mast cells mediators.[107-109] Electrophysiological studies have reported that mast cell mediators and IL-1 activate afferent vagal fibres (Figure 1).[108,110,111] Furthermore, both IV and IP administration of endotoxin induced c-Fos activity in primary afferent ganglia (i.e. nodose ganglia)[112] followed by increased NTS and splenic activity.[104] The same c-Fos induction was observed in the NTS in response to intestinal anaphylaxis and inflammation caused by surgical manipulation of the gut.[113-115] Subdiaphragmatic vagotomy largely abolishes c-Fos activity in NTS and DMV after i.p. injection of endotoxin (i.e. LPS and SEB).[105,116] Together, these observations strongly indicate that the brain is able to modulate the splenic immune response indirectly via the detection of circulating cytokines and directly via afferent input from sensory fibres.

Efferent arch of CAIP

The splenic immune response plays an important role during systemic inflammation, since splenic macrophages are the major source of TNF-α in sepsis.[117] Therefore, the spleen is considered to be the perfect target to modulate the immune response in response to endotoxemia. In light of this, Borovikova et al.[118] showed that vagus nerve stimulation (VNS) strongly inhibits splenic TNF-α production in a model of systemic inflammation, introducing the concept of the cholinergic anti-inflammatory pathway (CAIP). This anti-inflammatory response is mediated by the reduced activation of splenic macrophages expressing alpha7 nicotinic receptor (α7nAChR). Acetylcholine (ACh) released by memory T cells, namely, interacts with α7nAChR and inhibits the secretion of pro-inflammatory cytokines via the JAK-STAT pathway.[119-122]

Over the years, many studies have demonstrated the beneficial effect of VNS in other inflammatory models such as haemorrhagic shock,[123] pancreatitis[124] and collagen-induced arthritis.[125] Ourselves and others also extended the concept of CAIP to the GI tract, since the gut is largely innervated by the vagus nerve. Indeed, we and others showed that electrical, nutritional and pharmacological activation of the vagal pathway prevents surgical induced inflammation and thus postoperative ileus (POI).[122,126-129] CAIP activation also reduced intestinal inflammation in other models: diabetic-induced gastroparesis,[130] colitis,[131-133] and LPS-induced septic ileus.[134-137] In contrast, vagotomised mice have a higher susceptibility to develop colitis after dextran sulphate sodium (DSS) administration.[132,138,139] Moreover, a more severe colitis is also correlated with a reduction of mucosal levels of ACh in a model of depression.[132,140,141] Like in the spleen, the anti-inflammatory response of CAIP is mediated through α7nAChR macrophages. Deficiency of α7nAChR in bone marrow-derived cells significantly abrogated the vagal anti-inflammatory effect, whereas α7nAChR deficiency in neurons and other cells did not have a significant effect in POI, indicating that the beneficial effect of VNS depends on α7nAChR expression on immune cells rather on neuronal cells.[129,142] As in the spleen, the CAIP is not mediated by direct interaction between α7nAChR macrophages and efferent vagal fibres, but rather via the modulation of cholinergic enteric neurons in proximity of intestinal α7nAChR expressing macrophages.[113,129] Other mucosal and submucosal immune cells, such as dendritic cells, mast cells, and T and B lymphocytes also express nicotinic receptors and may, therefore, be involved in CAIP.[141]

CONCLUSION

To date, electrical stimulation of the vagus nerve is already used as a therapeutic tool for intractable epilepsy and treatment-resistant depression. Currently, the anti-inflammatory effects of VNS are explored in three clinical trials in patients with rheumatoid arthritis (RA), Crohn's disease and postoperative ileus (NCT01552941, NCT01569503 and NCT01572155). Future insight from clinical trials and from basic research will hopefully offer the cholinergic anti-inflammatory pathway as a novel and powerful new therapeutic tool.

REFERENCES

1. Drake RL et al. Gray's atlas of anatomy 1st ed (2008). Philadelphia: Churchill Livingstone, pp. xvi,558.

2. Tekdemir I et al. A clinico-anatomic study of the auricular branch of the vagus nerve and Arnold's ear-cough reflex. Surg Radiol Anat: SRA. 1998;20(4):253-7.

3. Yang AC et al. A new choice for the treatment of epilepsy: electrical auricula-vagus-stimulation. Med Hypotheses. 2011;77(2):244-5.

4. Schachter SC, Saper CB. Vagus nerve stimulation. Epilepsia. 1998;39(7):677-86.

5. Jackson RG. Anatomy of the vagus nerves in the region of the lower esophagus and the stomach. Anat Rec. 1949;103(1):1-18.

6. McCrea ED. The abdominal distribution of the vagus. J Anat. 1924;59(Pt 1):18-40.

7. Bayliss WM, Starling EH. The movements and the innervation of the large intestine. J Physiol. 1900;26(1-2):107-18.

8. Bourne GH, International Society for Cell Biology. International review of cytology (1952), New York: Academic Press, p. V.

9. Dorofeeva AA et al. Involvement of the sacral parasympathetic nucleus in the innervation of the descending colon and rectum in cats. Neurosci Behav Physiol. 2009;39(2):207-10.

10. Hansen JT et al. Netter's clinical anatomy 1st ed (2005), Philadelphia: Elsevier Inc, pp. ix,668.

11. Berthoud HR, Patterson LM. Anatomical relationship between vagal afferent fibers and CCK-immunoreactive entero-endocrine cells in the rat small intestinal mucosa. Acta Anat (Basel). 1996;156(2):123-31.

12. Berthoud HR, Neuhuber WL. Functional and chemical anatomy of the afferent vagal system. Auton Neurosci. 2000;85(1-3):1-17.

13. Rodrigo J et al. Vegetative innervation of the esophagus. II. Intraganglionic laminar endings. Acta Anat (Basel). 1975;92(1):79-100.

14. Berthoud HR, Powley TL. Vagal afferent innervation of the rat fundic stomach: morphological characterization of the gastric tension receptor. J Comp Neurol. 1992;319(2):261-76.

15. Powley TL, Phillips RJ. Vagal intramuscular array afferents form complexes with interstitial cells of Cajal in gastrointestinal smooth muscle: analogues of muscle spindle organs? Neuroscience. 2011;186:188-200.

16. Cailotto C et al. Immunohistochemical Study Evaluating the Vagal Innervation of Intestinal Resident Macrophages. Gastroenterology. 2011;140(5):S-370.

17. Berthoud HR et al. Topography of efferent vagal innervation of the rat gastrointestinal tract. Am J Physiol. 1991;260(1 Pt 2):R200-7.

18. Berthoud HR et al. Simultaneous labeling of vagal innervation of the gut and afferent projections from the visceral forebrain with dil injected into the dorsal vagal complex in the rat. J Comp Neurol. 1990;301(1):65-79.

19. Holst MC et al. Vagal preganglionic projections to the enteric nervous system characterized with Phaseolus vulgaris–leucoagglutinin. J Comp Neurol. 1997;381(1):81-100.

20. Schemann M, Grundy D. Electrophysiological identification of vagally innervated enteric neurons in guinea pig stomach. Am J Physiol. 1992;263(5 Pt 1):G709-18.

21. Berthoud HR et al. Vagal-enteric interface: vagal activation-induced expression of c-Fos and p-CREB in neurons of the upper gastrointestinal tract and pancreas. Anat Rec. 2001;262(1):29-40.

22. Zheng H, Berthoud HR. Functional vagal input to gastric myenteric plexus as assessed by vagal stimulation-induced Fos expression. Am J Physiol Gastrointest Liver Physiol. 2000;279(1):G73-81.

23. Lal S et al. Vagal afferent responses to fatty acids of different chain length in the rat. Am J Physiol Gastrointest Liver Physiol. 2001;281(4):G907-15.

24. Cummings DE, Overduin J. Gastrointestinal regulation of food intake. J Clin Invest. 2007;117(1):13-23.

25. Buyse M et al. Expression and regulation of leptin receptor proteins in afferent and efferent neurons of the vagus nerve. Eur J Neurosci. 2001;14(1):64-72.

26. Moriarty P et al. Characterization of cholecystokininA and cholecystokininB receptors expressed by vagal afferent neurons. Neuroscience. 1997;79(3):905-13.

27. Wang Y et al. Two types of leptin-responsive gastric vagal afferent terminals: an in vitro single-unit study in rats. Am J Physiol. 1997;273(2):R833-7.

28. Laughton WB, Powley TL. Localization of efferent function in the dorsal motor nucleus of the vagus. Am J Physiol. 1987;252(1 Pt 2):R13-25.

29. Wyrwicka W, Garcia R. Effect of electrical stimulation of the dorsal nucleus of the vagus nerve on gastric acid secretion in cats. Exp Neurol. 1979;65(2):315-25.

30. Ionescu E et al. Increases in plasma insulin levels in response to electrical stimulation of the dorsal motor nucleus of the vagus nerve. Endocrinology. 1983;112(3):904-10.

31. Berthoud HR et al. Localization of vagal preganglionics that stimulate insulin and glucagon secretion. Am J Physiol. 1990;258(1 Pt 2):R160-8.

32. Berthoud HR, Powley TL. Characteristics of gastric and pancreatic responses to vagal stimulation with varied frequencies: evidence for different fiber calibers? J Auton Nerv Syst. 1987;19(1):77-84.

33. Bergman RN, Miller RE. Direct enhancement of insulin secretion by vagal stimulation of the isolated pancreas. Am J Physiol. 1973;225(2):481-6.

34. Kaneto A et al. Effects of stimulation of the vagus nerve on insulin secretion. Endocrinology. 1967;80(3):530-6.

35. Kaneto A et al. Effects of vagal stimulation on glucagon and insulin secretion. Endocrinology. 1974;95(4):1005-10.

36. Bloom SR, Edwards AV. Pancreatic endocrine responses to stimulation of the peripheral ends of the vagus nerves in conscious calves. J Physiol. 1981;315:31-41.

37. Nishi S et al. Vagal regulation of insulin, glucagon, and somatostatin secretion in vitro in the rat. J Clin Invest. 1987;79(4):1191-6.

38. Berthoud HR et al. Evidence for a role of the gastric, coeliac and hepatic branches in vagally stimulated insulin secretion in the rat. J Auton Nerv Syst. 1983;7(2):97-110.

39. Bladin PH et al. Elevation of plasma gastrin and pancreatic polypeptide by electrical vagal stimulation in sheep: effects of sequential stimulation. Regul Pept. 1983;6(2):89-97.

40. Schwartz TW et al. Vagal, cholinergic regulation of pancreatic polypeptide secretion. J Clin Invest. 1978;61(3):781-9.

41. Frohman LA et al. Effect of vagotomy and vagal stimulation on insulin secretion. Diabetes. 1967;16(7):443-8.

42. Allen J et al. Acute rise of pancreatic polypeptide after electroconvulsive therapy. Br J Psychiatry. 1982;141(1):24-6.

43. Snoek SA et al. The enteric nervous system as a regulator of intestinal epithelial barrier function in health and disease. Expert Rev Gastroenterol Hepatol. 2010;4(5):637-51.

44. Bado A et al. The stomach is a source of leptin. Nature. 1998;394(6695):790-3.

45. Smith GP et al. The satiety effect of cholecystokinin: a progress report. Peptides. 1981;2 Suppl 2:57-9.

46. Berthoud HR et al. Vagal afferent innervation of rat abdominal paraganglia as revealed by anterograde DiI-tracing and confocal microscopy. Acta Anat (Basel). 1995;152(2):127-32.

47. Schwartz GJ et al. Pharmacological dissociation of responses to CCK and gastric loads in rat mechanosensitive vagal afferents. Am J Physiol. 1994;267(1):R303-8.

48. Widdop RE et al. Electrophysiological and autoradiographical evidence for cholecystokinin A receptors on rat isolated nodose ganglia. J Auton Nerv Syst. 1994;46(1):65-73.

49. Barrachina MD et al. Synergistic interaction between leptin and cholecystokinin to reduce short-term food intake in lean mice. Proc Natl Acad Sci USA. 1997;94(19):10455-60.

50. Emond M et al. Central leptin modulates behavioral and neural responsivity to CCK. Am J Physiol. 1999;276(5):R1545-9.

51. Zittel TT et al. C-fos protein expression in the nucleus of the solitary tract correlates with cholecystokinin dose injected and food intake in rats. Brain Res. 1999;846(1):1-11.

52. Peters JH et al. Cooperative activation of cultured vagal afferent neurons by leptin and cholecystokinin. Endocrinology. 2004;145(8):3652-7.

53. Peters J et al. Leptin and CCK selectively activate vagal afferent neurons innervating the stomach and duodenum. Am J Physiol Regul Integr Comp Physiol. 2006;290(6):R1544-9.

54. Forster E et al. Gastric emptying in rats: role of afferent neurons and cholecystokinin. Am J Physiol. 1990;258(4):G552-6.

55. Holzer HH et al. Intestinal lipid inhibits gastric emptying via CCK and a vagal capsaicin-sensitive afferent pathway in rats. Am J Physiol. 1994;267(4):G625-9.

56. Raybould HE, Tache Y. Cholecystokinin inhibits gastric motility and emptying via a capsaicin-sensitive vagal pathway in rats. Am J Physiol. 1988;255(2):G242-6.

57. Garlicki J et al. Cholecystokinin receptors and vagal nerves in control of food intake in rats. Am J Physiol. 1990;258(1):E40-5.

58. Li Y, Owyang C. Vagal afferent pathway mediates physiological action of cholecystokinin on pancreatic enzyme secretion. J Clin Invest. 1993;92(1):418.

59. Hildebrand P et al. Effects of a cholecystokinin receptor antagonist on intestinal phase of pancreatic and biliary responses in man. J Clin Invest. 1990;85(3):640-6.

60. Reidelberger RD, O'Rourke MF. Potent cholecystokinin antagonist L 364718 stimulates food intake in rats. Am J Physiol. 1989;257(6):R1512-8.

61. Green T et al. Action of the cholecystokinin antagonist L364, 718 on gastric emptying in the rat. Am J Physiol. 1988;255(5):G685-9.

62. Lotti VJ et al. In vivo pharmacology of L-364,718, a new potent nonpeptide peripheral cholecystokinin antagonist. J Pharmacol Exp Ther. 1987;241(1):103-9.

63. Raybould HE et al. Reflex decreases in intragastric pressure in response to cholecystokinin in rats. Am J Physiol. 1987;253(2):G165-70.

64. Smith GP et al. Abdominal vagotomy blocks the satiety effect of cholecystokinin in the rat. Science. 1981;213(4511):1036-7.

65. Berthoud HR et al. Distribution and structure of vagal afferent intraganglionic laminar endings (IGLEs) in the rat gastrointestinal tract. Anat Embryol (Berl). 1997;195(2):183-91.

66. Wang FB, Powley TL. Topographic inventories of vagal afferents in gastrointestinal muscle. J Comp Neurol. 2000;421(3):302-24.

67. Neuhuber WL. Sensory vagal innervation of the rat esophagus and cardia: a light and electron microscopic anterograde tracing study. J Auton Nerv Syst. 1987;20(3):243-55.

68. Berthoud HR et al. Neuroanatomy of extrinsic afferents supplying the gastrointestinal tract. Neurogastroenterol Motil. 2004;16 Suppl 1:28-33.

69. Song X et al. Identification of medium/high-threshold extrinsic mechanosensitive afferent nerves to the gastrointestinal tract. Gastroenterology. 2009;137(1):274-84.

70. Zagorodnyuk VP, Brookes SJ. Transduction sites of vagal mechanoreceptors in the guinea pig esophagus. J Neurosci. 2000;20(16):6249-55.

71. Zagorodnyuk VP et al. Intraganglionic laminar endings are mechano-transduction sites of vagal tension receptors in the guinea-pig stomach. J Physiol. 2001;534(Pt 1):255-68.

72. Wang F, Powley T, editors. Taxonomy of vagal afferent projections to the gastrointestinal tract. Soc Neurosci Abstr; 1994.

73. Powley T et al. Ultrastructural evidence for communication between intramuscular vagal mechanoreceptors and interstitial cells of Cajal in the rat fundus. Neurogastroenterol Motil. 2008;20(1):69-79.

74. Kressel M et al. Vagal innervation of the rat pylorus: an anterograde tracing study using carbocyanine dyes and laser scanning confocal microscopy. Cell Tissue Res. 1994;275(1):109-23.

75. Neuhuber WL et al. Vagal efferent and afferent innervation of the rat esophagus as demonstrated by anterograde DiI and DiA tracing: focus on myenteric ganglia. J Auton Nerv Syst. 1998;70(1-2):92-102.

76. Phillips RJ et al. Afferent innervation of gastrointestinal tract smooth muscle by the hepatic branch of the vagus. J Comp Neurol. 1997;384(2):248-70.

77. Cannon WB, Lieb CW. The receptive relaxation of the stomach. Am J Physiol. 1911;29(2):267-73.

78. Andrews PL et al. Reflex excitation of antral motility induced by gastric distension in the ferret. J Physiol. 1980;298:79-84.

79. Davison J, Clarke G. Mechanical properties and sensitivity to CCK of vagal gastric slowly adapting mechanoreceptors. Am J Physiol. 1988;255(1):G55-61.

80. Schwartz GJ et al. Integration of vagal afferent responses to gastric loads and cholecystokinin in rats. Am J Physiol. 1991;261(1):R64-9.

81. Schwartz GJ et al. Gastric loads and cholecystokinin synergistically stimulate rat gastric vagal afferents. Am J Physiol. 1993;265(4 Pt 2):R872-6.

82. Schwartz GJ et al. Gastric loads potentiate inhibition of food intake produced by a cholecystokinin analogue. Am J Physiol. 1991;261(5 Pt 2):R1141-6.

83. Moran TH, McHugh PR. Cholecystokinin suppresses food intake by inhibiting gastric emptying. Am J Physiol. 1982;242(5):R491-7.

84. Grundy D et al. Inhibition of gastric mechanoreceptor discharge by cholecystokinin in the rat. Am J Physiol. 1995;268(2 Pt 1):G355-60.

85. Shen L, Turner JR. Role of epithelial cells in initiation and propagation of intestinal inflammation. Eliminating the static: tight junction dynamics exposed. Am J Physiol Gastrointest Liver Physiol. 2006;290(4):G577-82.

86. Bansal V et al. Traumatic brain injury and intestinal dysfunction: uncovering the neuro-enteric axis. J Neurotrauma. 2009;26(8):1353-9.

87. Costantini TW et al. Burn-induced gut barrier injury is attenuated by phosphodiesterase inhibition: effects on tight junction structural proteins. Shock. 2009;31(4):416.

88. Reys LG et al. Uncovering the neuroenteric-pulmonary axis: vagal nerve stimulation prevents acute lung injury following hemorrhagic shock. Life Sci. 2013;92(13):783-92.

89. Costantini TW et al. Efferent vagal nerve stimulation attenuates gut barrier injury after burn: modulation of intestinal occludin expression. J Trauma. 2010;68(6):1349-54; discussion 1354-6.

90. Krzyzaniak M et al. Postinjury vagal nerve stimulation protects against intestinal epithelial barrier breakdown. J

Trauma. 2011;70(5):1168-75; discussion 75-6.

91. de Haan JJ et al. Protection against early intestinal compromise by lipid-rich enteral nutrition through cholecystokinin receptors. Crit Care Med. 2010;38(7):1592-7.

92. Krzyzaniak MJ et al. Efferent vagal nerve stimulation attenuates acute lung injury following burn: The importance of the gut-lung axis. Surgery. 2011;150(3):379-89.

93. Krzyzaniak M et al. Postinjury vagal nerve stimulation protects against intestinal epithelial barrier breakdown. J Trauma. 2011;70(5):1168-75.

94. Levy G et al. Parasympathetic stimulation via the vagus nerve prevents systemic organ dysfunction by abrogating gut injury and lymph toxicity in trauma and hemorrhagic shock. Shock. 2013;39(1):39-44.

95. Lubbers T et al. Cholecystokinin/Cholecystokinin-1 receptor-mediated peripheral activation of the afferent vagus by enteral nutrients attenuates inflammation in rats. Ann Surg. 2010;252(2):376-82.

96. Luyer MD et al. Parasympathetic stimulation via the vagus nerve prevents systemic organ dysfunction by abrogating gut injury and lymph toxicity in trauma and hemorrhagic shock. Shock. 2013;39(5):460-1.

97. Cheadle GA et al. Enteric glia cells attenuate cytomix-induced intestinal epithelial barrier breakdown. PloS one. 2013;8(7):e69042.

98. Savidge TC et al. Enteric glia regulate intestinal barrier function and inflammation via release of S-nitrosoglutathione. Gastroenterology. 2007;132(4):1344-58.

99. Costantini TW et al. Vagal nerve stimulation protects against burn-induced intestinal injury through activation of enteric glia cells. Am J Physiol Gastrointest Liver Physiol. 2010;299(6):G1308-18.

100. Costantini TW et al. Targeting alpha-7 nicotinic acetylcholine receptor in the enteric nervous system: a cholinergic agonist prevents gut barrier failure after severe burn injury. The Am J Pathol. 2012;181(2):478-86.

101. Sternberg EM. Neural regulation of innate immunity: a coordinated nonspecific host response to pathogens. Nat Rev Immunol. 2006;6(4):318-28.

102. Elmquist JK et al. Distribution of Fos-like immunoreactivity in the rat brain following intravenous lipopolysaccharide administration. J Comp Neurol. 1996;371(1):85-103.

103. Hermann GE et al. c-Fos generation in the dorsal vagal complex after systemic endotoxin is not dependent on the vagus nerve. Am J Physiol Regul integr Comp Physiol. 2001;280(1):R289-99.

104. Buijs RM et al. Spleen vagal denervation inhibits the production of antibodies to circulating antigens. PloS one. 2008;3(9):e3152.

105. Wan W et al. Neural and biochemical mediators of endotoxin and stress-induced c-fos expression in the rat brain. Brain Res Bull. 1994;34(1):7-14.

106. Goehler LE et al. Vagal immune-to-brain communication: a visceral chemosensory pathway. Auton Neurosci. 2000;85(1-3):49-59.

107. Ek M et al. Activation of vagal afferents after intravenous injection of interleukin-1beta: role of endogenous prostaglandins. J Neurosci. 1998;18(22):9471-9.

108. Undem BJ et al. Immunologically induced neuromodulation of guinea pig nodose ganglion neurons. J Auton Nerv Syst. 1993;44(1):35-44.

109. Greene R et al. IgE-challenged human lung mast cells excite vagal sensory neurons in vitro. J Appl Physiol. 1988;64(5):2249-53.

110. Niijima A. The afferent discharges from sensors for interleukin 1 beta in the hepatoportal system in the anesthetized rat. J Auton Nerv Syst. 1996;61(3):287-91.

111. Goehler LE et al. Interleukin-1 induces c-Fos immunoreactivity in primary afferent neurons of the vagus nerve. Brain Res. 1998;804(2):306-10.

112. Gaykema RP et al. Bacterial endotoxin induces fos immunoreactivity in primary afferent neurons of the vagus nerve. Neuroimmunomodulation. 1998;5(5):234-40.

113. Cailotto C et al. Neuroanatomical evidence demonstrating the existence of the vagal anti-inflammatory reflex in the intestine. Neurogastroenterology Motil. 2012;24(2):191-200, e93.

114. Castex N et al. c-fos expression in specific rat brain nuclei after intestinal anaphylaxis: involvement of 5-HT3 receptors and vagal afferent fibers. Brain Res. 1995;688(1-2):149-60.

115. van Bree SH et al. Systemic inflammation with enhanced brain activation contributes to more severe delay in postoperative ileus. Neurogastroenterol Motil. 2013;25(8):e540-9.

116. Wang X et al. Fos expression in the rat brain after intraperitoneal injection of Staphylococcus enterotoxin B and the effect of vagotomy. Neurochem Res. 2004;29(9):1667-74.

117. Rosas-Ballina M et al. Splenic nerve is required for cholinergic antiinflammatory pathway control of TNF in endotoxemia. Proc Natl Acad Sci U S A. 2008;105(31):11008-13.

118. Borovikova LV et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature. 2000;405(6785):458-62.

119. Wang H et al. Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. Nature. 2003;421(6921):384-8.

120. Rosas-Ballina M et al. Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit. Science. 2011;334(6052):98-101.

121. Vida G et al. a7-cholinergic receptor mediates vagal induction of splenic norepinephrine. J Immunol. 2011;186(7):4340-6.

122. de Jonge WJ et al. Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-STAT3 signaling pathway. Nat Immunol. 2005;6(8):844-51.

123. Guarini S et al. Efferent vagal fibre stimulation blunts nuclear factor-kappaB activation and protects against hypovolemic hemorrhagic shock. Circulation. 2003;107(8):1189-94.

124. van Westerloo DJ et al. The vagus nerve and nicotinic receptors modulate experimental pancreatitis severity in mice. Gastroenterology. 2006;130(6):1822-30.

125. Zhang P et al. Inhibition of the development of collagen-induced arthritis in Wistar rats through vagus nerve suspension: a 3-month observation. Inflamm Res. 2008;57(7):322-8.

126. The FO et al. Activation of the cholinergic anti-inflammatory pathway ameliorates postoperative ileus in mice. Gastroenterology. 2007;133(4):1219-28.

127. The F et al. Central activation of the cholinergic anti-inflammatory pathway reduces surgical inflammation in experimental post-operative ileus. Br J Pharmacol. 2011;163(5):1007-16.

128. Lubbers T et al. Lipid-rich enteral nutrition reduces postoperative ileus in rats via activation of cholecystokinin-receptors. Ann Surg. 2009;249(3):481-7.

129. Matteoli G et al. A distinct vagal anti-inflammatory pathway modulates intestinal muscularis resident macrophages independent of the spleen. Gut. 2013. doi:10.1136/gutjnl-2012-304676. [Epub ahead of print].

130. Choi KM et al. CD206-positive M2 macrophages that express heme oxygenase-1 protect against diabetic gastroparesis in mice. Gastroenterology. 2010;138(7):2399-409.

131. Ghia JE et al. The protective effect of the vagus nerve in a murine model of chronic relapsing colitis. Am J Physiol Gastrointest Liver Physiol. 2007;293(4):G711-8.

132. Ghia JE et al. Impaired parasympathetic function increases susceptibility to inflammatory bowel disease in a mouse model of depression.

J Clin Invest. 2008;118(6):2209-18.

133. Rosas-Ballina M, Tracey KJ. The neurology of the immune system: neural reflexes regulate immunity. Neuron. 2009;64(1):28-32.

134. Turler A et al. MCP-1 causes leukocyte recruitment and subsequently endotoxemic ileus in rat. Am J Physiol Gastrointest Liver Physiol. 2002;282(1):G145-55.

135. Eskandari MK et al. LPS-induced muscularis macrophage nitric oxide suppresses rat jejunal circular muscle activity. Am J Physiol. 1999;277(2 Pt 1):G478-86.

136. Eskandari MK et al. Lipopolysaccharide activates the muscularis macrophage network and suppresses circular smooth muscle activity. The American journal of physiology. 1997;273(3 Pt 1):G727-34.

137. de Winter BY et al. Role of oxidative stress in the pathogenesis of septic ileus in mice. Neurogastroenterol Motil. 2005;17(2):251-61.

138. O'Mahony C et al. Loss of vagal anti-inflammatory effect: in vivo visualization and adoptive transfer. Am J Physiol Regul Integr Comp Physiol. 2009;297(4):R1118-26.

139. Ghia JE et al. The vagus nerve: a tonic inhibitory influence associated with inflammatory bowel disease in a murine model. Gastroenterology. 2006;131(4):1122-30.

140. Ghia JE et al. Reactivation of inflammatory bowel disease in a mouse model of depression. Gastroenterology. 2009;136(7):2280-8 e1-4.

141. Matteoli G, Boeckxstaens GE. The vagal innervation of the gut and immune homeostasis. Gut. 2013;62(8):1214-22.

142. Olofsson PS et al. a7 nicotinic acetylcholine receptor (alpha7nAChR) expression in bone marrow-derived non-T cells is required for the inflammatory reflex. Mol Med. 2012;18:539-43.

A REVIEW OF CROHN'S DISEASE

Philip Hendy,[1] Ailsa Hart[2]

1. Gastroenterology SPR, St Mark's Hospital, Middlesex, UK
2. Gastroenterology Consultant, St Mark's Hospital, Middlesex, UK

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ABSTRACT

Crohn's disease is a chronic relapsing inflammatory bowel disease that may affect any part of the gastrointestinal tract. The ileum, colon, and perineum are most commonly affected. It is characterised by transmural inflammation, and granulomata may be present. Whilst the aetiology of Crohn's disease is not completely understood, it is thought to be caused by the complex interplay between genetic, immunological, microbiological, and environmental factors. Current opinion is that, in genetically susceptible individuals, there is an immune dysregulation to an environmental factor, and the intestinal microbiota plays a central role. Genetic studies of patients with Crohn's disease have found several gene mutations which affect the innate immune system. Two important mutations contributing towards the pathogenesis of Crohn's disease are Nucleotide-binding oligomerisation domain-containing protein 2 (NOD2) and autophagy-related 16-like 1 (ATG16L1). The most common symptoms of Crohn's disease are diarrhoea, abdominal pain, weight loss, and fatigue. Symptoms reflect the site and behaviour of disease, and the presence or absence of strictures and fistulae. Extraintestinal manifestations may be present and typically affect the eyes, skin, joints, or biliary tree. Investigations are performed to map the disease location, assess disease severity, and survey for complications of the disease or treatment. Management is with smoking cessation, steroids, immunomodulators, anti-tumour necrosis factor (TNF) therapy, or surgery.

Keywords: Anti-tumour necrosis factor alpha (anti-TNFα), autophagy genes, Crohn's disease, immunomodulators, inflammatory bowel disease, metabolomics, metagenomics, NOD2.

INTRODUCTION

Crohn's disease is a chronic idiopathic condition characterised by relapsing inflammation of the bowel. Any level of the gastrointestinal tract may be affected from the mouth to the anus, with the ileum, colon and perineum most frequently involved. Extraintestinal manifestations (EIMs) may occur and can affect the skin, joints, liver/biliary tree, and eyes.

Crohn's disease can cause significant morbidity with symptoms including abdominal pain, diarrhoea, faecal incontinence, rectal bleeding, weight loss, and fatigue. The prevalence is increasing in both the West and in the developing world. Crohn's disease particularly affects young adults at a time in life when they are in education, starting work or family lives, and it can have a major impact on quality of life.

EPIDEMIOLOGY

Crohn's disease is more common in the West than developing countries. Northern Europe and the USA have the highest rates of Crohn's disease.[1] In the West, there is also a north/south divide, with rates in Northern Europe of 7 per 100,000 person-years, compared with 3.9 in Southern Europe; with a similar pattern seen in Northern latitude USA compared with Southern latitude USA (hazard ratio 0.48 in the South).[2] Rates in the West have generally been increasing, but are now thought be to plateauing.[1]

Ethnicity also has an effect on presentation of Crohn's disease; in the USA, African Americans are more likely to have colonic and perianal disease and less likely to have ileal disease than their white counterparts. African Americans are also more likely to require hospitalisation as a result

of their Crohn's disease.[3,4] Rates in the East are increasing, especially in China and India.[5] Migrants from developing nations to the West develop rates above that of their birth country.[6] Jews, in particular Ashkenazi Jews, have a high prevalence.[7] There is a bimodal distribution of age at presentation, with the main peak at 10-40 years of age, with a smaller peak in the 60s.

AETIOLOGY

The aetiology of Crohn's disease is incompletely understood. It is known that immunological, microbiological, lifestyle, and genetic factors are implicated. Current opinion is that in genetically susceptible individuals, there is an immune dysregulation to an environmental factor, and the intestinal microbiota plays a central role.

GENETICS

Family history is a major risk factor for Crohn's disease. Having a first degree relative with the disease increases the risk 10-fold; and 9-15% of patients with Crohn's disease have an affected first degree relative. The highest risk is with monozygotic twins, where disease concordance is between 35-50%.[8] There has been major progress over the last decade in identifying susceptibility genes for Crohn's disease through Genome-wide Association studies (GWAS) and now over 160 independent susceptibility loci have been found. The first Crohn's disease gene identified was Nucleotide-binding oligomerisation domain-containing protein 2 (NOD2). NOD2 homozygotes have a 17-fold increased risk of developing Crohn's disease, whilst heterozygotes have a 2-fold increased risk. Interestingly, patients with Crohn's disease who originate from China and Japan do not have the NOD2 mutation.[9] Impaired autophagy[10] (self-digestion by a cell through the action of enzymes originating within the same cell) is increasingly implicated in the pathogenesis of Crohn's disease, and mutations at both NOD2 and autophagy-related 16-like 1 (ATG16L1) loci are associated with disrupted autophagy.

IMMUNOLOGY

Mutations at gene loci coding for immune molecules and pathways, identified via GWAS, have implicated a range of immunological 'culprits' involved in the pathogenesis of Crohn's. Defects in both the innate and adaptive immune systems are present in Crohn's disease. Barrier function, the first line of innate defence, is impaired by both an inadequate mucous layer, and by abnormally low levels of protective antimicrobial peptides (such as the human α-defensin produced in health by Paneth cells), which admit greater antigenic and microbial exposure to the epithelium. Dendritic cells, with their ability to control tolerogenicity are the key link between the innate and adaptive immune systems. Dendritic cell distribution, expression of toll-like receptors, co-stimulatory markers and homing markers, as well as secretion of cytokines, are all altered in Crohn's disease.[11,12] The role of the adaptive immune system in Crohn's disease is characterised by an imbalance between pro-inflammatory effector cells such as Th1 and Th17 (secreting pro-inflammatory mediators including IL12, IL17 and Tumour necrosis factor alpha [TNFα]) and regulatory cells including Tr1 and Th3 (secreting regulatory cytokines such as IL10 and transforming growth factor-beta [TGFβ]).

ENVIRONMENTAL FACTORS

Smoking

Smoking is an independent risk factor for developing Crohn's disease, and has been widely studied. For patients with Crohn's disease, smoking increases progression to more advanced disease (stricturing and/or penetrating); and cessation of smoking is associated with a reduction in progression to advanced disease, and a reduced need for surgery.[13,14]

Diet

Since diet provides the bulk of the antigenic stream that passes through the intestine it would seem likely that dietary factors are relevant in the aetiology of Crohn's disease. However, no food component has yet been proven to be clearly implicated in the pathogenesis. Elemental and polymeric diets, both with lower antigenic load than a normal diet, are successful treatments for Crohn's disease in children. A recent large population-based study has shown that high intake of long chain 3-PUFA (n3-polyunsaturated fatty acid) may be protective against ulcerative colitis (UC), whilst high intake of transunsaturated fats may predispose to disease. The data were not significant for Crohn's disease.[15]

Microbiome

The microbiome consists of billions of microorganisms that line the intestinal mucosa. The composition of the flora within the microbiome is affected by host and environmental factors (diet, antibiotics, etc.). The converse is true also, with the microbiome able to alter mucosal cell DNA sequences. The sheer size of the microbiome, together with its important symbiosis with intestinal immunity, has led to some observers calling the microbiome an organ in its own right. Modern techniques, especially high resolution mass spectroscopy and nuclear magnetic resonance, have enabled detailed study of the constituents of the microbiome. Developments in the field of metabolomics[16] may allow detection of specific microorganism products, through the recognition of unique chemical signatures in waste products such as urine or faeces.

Metagenomic sequencing (analysis of the DNA content of an entire environmental system – in this case the microbiome) is another evolving area of research that is adding to our understanding of the composition of the microbiome.[17] From these studies it is known that the ratio of numbers of bacteria of the four main phyla differ when comparing active Crohn's disease with healthy controls. Reduced firmicute (especially *Faecalibacterium prausnitzii*) and *bacteroides spp*. organism ratios are associated with disease. The use of metagenomic and metabolomic techniques to compare gut microbiota composition in health and in disease has unearthed potential pathogenic pathways, and it is hoped that novel biomarkers of disease will be revealed. Clinically, the importance of the microbiome for driving inflammation is demonstrated by the healing of downstream mucosa after diversion surgery in Crohn's disease, and the recurrence of inflammation after continuity is restored.

PATHOPHYSIOLOGY

Crohn's disease is characterised by transmural inflammation of any part of the gastrointestinal (GI) tract. The most common disease locations are the distal ileum, the colon, and the perineum, indeed it is unusual to have isolated disease elsewhere in the absence of involvement of at least one of these sites. Multiple sites may be diseased, and the pattern of healthy mucosa between diseased segments is termed 'skip lesions' and is typical of Crohn's disease. The deep inflammation allows penetrating (fistulising) and stricturing disease. Histologically the disease is recognised by transmural inflammation, with lymphocyte and plasma cell infiltration, crypt disruption and the presence of non-caseating granulomas.

CLINICAL PRESENTATION

The symptoms are largely dictated by disease location and the presence or absence of strictures and fistulae. Since there are multiple possible disease sites, the presenting feature may be very varied. The most common presenting symptoms are diarrhoea, weight loss, abdominal pain, and fatigue. The Montreal system (Table 1) is used to classify the disease, and the features included are important in determining prognosis and optimal therapy.

EIMs predominantly affect the skin (erythema nodosum, pyoderma gangrenosum), the joints (small joint polyarthropathy, large joint arthropathy, ankylosing spondylitis), the eyes (episcleritis, scleritis and uveitis), and the biliary tree (primary sclerosing cholangitis [PSC]). Patients with Crohn's disease also have an increased risk of venous thromboembolic disease, colorectal cancer (CRC),[18] gallstones, renal stones, and osteoporosis. Recently, an increased risk of malignant melanoma[19] (MM) has been identified, independent of immune suppressant medication

Table 1. Montreal classification of Crohn's disease.

Age at diagnosis	Location	Behaviour
A1: <16 years	L1: Ileal	B1: Inflammatory
A2: 17-40 years	L2: Colonic	B2: Stricturing
A3: >40 years	L3: Ileocolonic	B3: Penetrating
	L4: Upper GI disease	P: Perianal disease

(azathioprine is known to increase the risk of non-MM skin cancers). Optimal skin protection in the sun is imperative.

The increased risk of CRC secondary to chronic colonic inflammation has necessitated implementation of colonoscopic surveillance. The interval between surveillance endoscopies is dictated by the presence or absence of other risk factors and is usually every 1, 3 or 5 years. Other pertinent risks factors include disease severity, disease extent, family history of CRC, presence of post-inflammatory polyps, PSC, dysplasia, and previous colonic stricture.

DIAGNOSIS

Crohn's disease is a clinical diagnosis that relies on history and examination, in combination with laboratory, radiological, and histological investigations. The history must include: type, onset, duration, and severity of symptoms; as well as past-medical, drug, and family histories. The physical examination should include BMI, abdominal examination (especially for tenderness and right iliac fossae masses), perineal and rectal examinations, as well as assessment for EIMs. It is important to consider differential diagnoses; especially mycobacterial disease, where the standard immunosuppressive therapy for Crohn's disease might cause a significant progression of tuberculosis infection.

Laboratory Tests

Full blood count, renal function, liver function, albumin, and inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) are all mandatory tests. Anaemia and thrombocytosis are common findings. Anaemia may be due to deficiencies of iron, folate or vitamin B12. Stool tests should include microscopy and culture; *Clostridium difficile* toxin assay and faecal granulocyte proteins (calprotectin or lactoferrin). Infection is a readily treatable precipitant of exacerbations of Crohn's disease, and therefore it is important to screen for infection with every flare. Faecal granulocyte proteins were initially used to distinguish IBS from organic bowel pathologies. More recently, their ability to predict disease relapse has led to their use in clinical decision-making about escalation and withdrawal of treatment, and about the need for endoscopy. For example, when assessing disease activity in a patient on anti-TNF, a high faecal calprotectin value is predictive of disease relapse and might dissuade the clinician from withdrawing the anti-TNF.[20]

Endoscopy

Ileocolonoscopy with biopsies is the gold standard investigation for diagnosing Crohn's disease, for assessment of disease activity and for surveillance for dysplasia and cancer. Typical endoscopic features include isolated aphthous ulcers, cobblestoning, and deep ulceration. The presence of deep ulceration indicates severe disease whilst post-inflammatory polyps (pseudo-polyps) suggest previous severe inflammation. Gastroscopy is recommended in children, or adults with upper gastrointestinal symptoms. Capsule endoscopy is well validated for small bowel Crohn's disease, and is used when other modalities have not provided a diagnosis.[21,22] It is sensitive,[23] but not specific,[24] and cannot provide a tissue diagnosis. Double balloon enteroscopy is sensitive for small bowel lesions,[25] and can obtain histological samples, but is expensive, time-consuming, frequently requires general anaesthesia, and is not available in all centres.

Imaging

Fluoroscopy (barium and Gastrografin® follow-through), which has long been the mainstay of abdominal imaging in Crohn's disease, has been superceded by CT and MR enterography (CTE and MRE), but still provides good images in skilled hands. CTE and MRE have similar diagnostic yield to one other.[26,27] The major advantage of MRE is the lack of ionising radiation which is important in a cohort of patients likely to need repeated imaging. Both modalities, CTE and MRE, may detect mucosal inflammation, strictures, dilated bowel, fistulae, and abscesses. A recent study showed MRE to be as good as CTE in detecting abdominal fistulae.[27] MR is superior for pelvic investigation, and does not involve ionising radiation (a significant consideration in a cohort of patients who require numerous cross-sectional scans), although lower radiation CT techniques are being introduced. Any combination of two of these three modalities offers the highest sensitivity.[28] Ultrasonography has the advantage of avoiding ionising radiation,[26] but is highly operator dependent.

Standard abdominal radiography is useful for emergency presentations as a quick, cheap, and easy test to assess small bowel dilatation and colonic inflammation.

VALIDATED DISEASE SEVERITY ASSESSMENT TOOLS

In clinical practice, probably the most frequently used assessment tool is the Harvey-Bradshaw Index (HBI) (Figure 1). Its popularity is linked to its simplicity, as it is comprised entirely of clinical parameters. Although somewhat subjective, it is used to assess disease activity and to aid treatment decision.

MANAGEMENT

Therapeutic goals include: induction and maintenance of clinical and endoscopic remission, swift resolution of exacerbations, maintenance of adequate nutrition, regular surveillance for complications, monitoring for and avoidance of adverse drug-induced effects, and optimising quality of life. A distinction must be made between inducing and maintaining remission. Steroids, for example, are effective at inducing remission, but lack of long-term efficacy alongside potent adverse effects render them unsuitable for maintenance therapy. Patient education is increasingly recognised to improve compliance with therapy. The type of therapy depends upon disease location and severity, the presence of complications, and lifestyle factors; as a result, treatment pathways must be individualised.

Some patients have a relatively benign disease course without developing significant complications, whilst others suffer chronic poor health and frequent complications. Risk stratification is vital to ensure that those with a benign disease course are not subject to the risks of over-treatment, and conversely to avoid unnecessary disease progression and complications through under-treating those with aggressive disease. Table 2 lists clinical, endoscopic and laboratory predictors of aggressive disease which, if present, should cause consideration of a more aggressive ('top-down') therapeutic approach at an early stage.[29]

Questions:

1. General wellbeing (0=very well, 1=slightly below average, 2=poor, 3=very poor, 4=terrible)
2. Abdominal pain (0=none, 1=mild, 2=moderate, 3=severe)
3. Number of liquid stools per day
4. Abdominal mass (0=none, 1=dubious, 2=definite, 3=tender)
5. Complications (1 point each)
   - Arthralgia
   - Uveitis
   - Erythema Nodosum
   - Aphthous Ulcers
   - Pyoderma Gangrenosum
   - Anal Fissure
   - New Fistula
   - Abscess

Results:

- <5 Remission
- 5-7 Mild Disease
- 8-16 Moderate Disease
- >16 Severe Disease

Figure 1. Harvey-Bradshaw Index.
A points-based scoring system used to aid with the assessment of severity of Crohn's disease.

Table 2. Clinical, endoscopic, and laboratory predictors of aggressive disease.

Predictor
Rectal/perianal disease
Extensive small bowel disease
Deep endoscopic ulceration
Young age
Active smoker
Steroids required at diagnosis
Serological markers – ASCA, OmpC, anti-I2, CBir1s[30]
Genetic – NOD2

Smoking

Cessation of smoking is an effective intervention in the treatment of Crohn's disease. Smoking predisposes to a more aggressive disease course, with stricturing and fistulising disease.[14,31]

Diet

Polymeric and elemental diets are effective at inducing remission in children, but less so in adults.[32] This may relate to compliance. A low residue diet helps prevent sub-acute bowel obstruction in patients with stricturing disease. Although diet may not treat Crohn's disease, nutritional assessment and supplementation are important.

Aminosalicylates

Published meta-analyses are inconsistent with regards to efficacy of 5-ASA in Crohn's disease. European guidelines are that 5-ASAs are not recommended for maintenance of medically-induced remission of Crohn's disease.[33] Sulphasalazine may be used for mild colonic disease and may be used in patients with joint symptoms. There may be a role for mesalazine in prevention of recurrence of post-operative Crohn's.[34]

Corticosteroids

Budesonide is first-line therapy for inducing remission of mild exacerbations of ileocaecal Crohn's disease.[35] It is associated with fewer adverse effects than systemic steroids such as prednisolone. Systemic steroids can be used for inducing remission during severe flares of ileocolonic Crohn's disease,[33] but anti-TNF drugs may be more appropriate. Steroids are not safe or efficacious for maintenance therapy.

Antibiotics, Probiotics, Prebiotics, and Faecal Transplantation

Ciprofloxacin and metronidazole are effective for treating septic complications of Crohn's disease and for perianal disease. The long-term sequelae of these two drugs include Achilles' tendon rupture and peripheral neuropathy, respectively. There is no convincing evidence that antibiotic therapy is effective in maintaining remission in Crohn's disease.[33,36] There are no data that probiotics, prebiotics or faecal transplantation provide any benefit in the treatment of Crohn's disease.

Immunomodulators

The thiopurines azathioprine and 6-mercaptopurine (6-MP) are widely used to maintain medically induced remission of moderate-to-severe Crohn's disease. Onset of action is slow, and full clinical response may take up to 16 weeks, therefore immunomodulators should not be used as single agent therapy, but should be used alongside a drug that induces rapid remission (e.g. corticosteroid or biological therapy). In patients who start to fail thiopurines therapy, thiopurine metabolites can be measured to ensure therapeutic dosing before considering a change in medication. Common adverse effects include nausea, vomiting, pancytopaenia, and pancreatitis. Mild-to-moderate drug side-effects would warrant a switch between thiopurine agents. A severe adverse reaction, such as acute pancreatitis, would be a contraindication to the further use of thiopurines. Methotrexate,

an anti-metabolite, is used in Crohn's disease. It is also effective at treating inflammatory bowel disease (IBD)-related arthropathy. Complications of drug treatment include nausea, bone marrow suppression, and fibrosis of the liver, lungs, and thyroid. Concomitant folic acid supplementation is important.

Anti-TNF Therapy

Monoclonal antibody therapy, including infliximab, adalimumab and certolizumab, is effective for induction and maintenance of remission of moderate-to-severe Crohn's disease.[37,38] Development of antibodies to the drug may impair efficacy, but incidence of antibody formation can be reduced by regular scheduled dosing[39] (as compared with ad hoc dosing) and by concomitant use of an immunomodulator.[29,40] Adverse effects of anti-TNF therapy include infusion reactions, local injection site reactions, demyelination, reactivation of latent infections (especially tuberculosis), and a potentially increased risk of malignancy. The absolute risk of lymphoma is 1.9/10,000 patient-years for a patient with Crohn's disease. With the addition of an immunomodulator the absolute risk is 3.6/10,000 patient-years, and with dual therapy (anti-TNF plus immunomodulator) the absolute risk is 6.1/10,000 patient-years.[41] In patients with no other risk factors for malignancy, the significant benefits of anti-TNF therapy may weigh favourably against this small increase in absolute risk. In patients with other risk factors for malignancy, especially past medical history and advancing age, the absolute risk is likely to be increased and the use of anti-TNF must be carefully considered.

New Agents

Natalizumab is a humanised monoclonal antibody against the cell adhesion molecule α4-integrin that has FDA approval. Therapies targeting inflammatory cytokines and homing molecules are also under investigation.

Surgery

Distal ileal resection can be considered for short segment moderate-to-severe disease. Extensive small bowel resection can lead to short bowel syndrome, and so intensification of medical therapy and trial of stricturoplasty are important to attempt to maintain bowel length. Surgery is also performed for perianal complications and includes laying open fistulae and seton insertion as well as drainage of abscesses.

PREGNANCY AND IBD

The highest peak of incidence of Crohn's disease is during the child bearing years, so questions about fertility, pregnancy, and breast-feeding are often asked by patients. Data suggest that whilst inactive Crohn's disease does not reduce fertility, active disease and previous abdominal or pelvic surgery are associated with decreased fertility. Patients with Crohn's disease have, on average, fewer children than healthy controls, but a large population-based trial showed that this is probably related to patient choice.[42]

The over-riding aim of therapy during pregnancy is to maintain remission. Active disease is associated with adverse pregnancy outcomes.[43,44] Steroids, 5-ASA, and azathioprine are probably safe in pregnancy,[45] but careful counselling of the family is important, and compliance should be encouraged through patient education. Anti-TNF therapy is also thought to be safe, although it does cross the placental barrier; if possible, doses should be avoided in the final trimester. Methotrexate and thalidomide are both highly teratogenic and are absolutely contraindicated in the period before conception (for the father as well as the mother) and during the pregnancy. Sulfasalazine is known to reduce sperm numbers and motility. Caesarean section should be considered for cases of active perianal disease.

REFERENCES

1. Loftus EV, Sandborn WJ. Epidemiology of inflammatory bowel disease. Gastroenterol Clin North Am. 2002;31:1-20.

2. Khalili H. et al. Geographical variation and incidence of inflammatory bowel disease among US women. Gut. 2012;61:1686-92.

3. Basu D et al. Impact of race and ethnicity on inflammatory bowel disease. Am J Gastroenterol. 2005;100:2254-61.

4. Nguyen GC et al. National estimates of the burden of inflammatory bowel disease among racial and ethnic groups in the United States. J Crohns Colitis. 2013;doi:10.1016/j.crohns.2013.09.001. [Epub ahead of print].

5. Ahuja V, Tandon RK. Inflammatory bowel disease in the Asia-Pacific area: a comparison with developed countries and regional differences. J Dig Dis. 2010;11:134–47.

6. Joossens M. et al. Contribution of genetic and environmental factors in the pathogenesis of Crohn's disease in a large family with multiple cases. Inflamm Bowel Dis. 2007;13:580–4.

7. Baumgart DC, Sandborn WJ. Crohn's disease. Lancet. 2012;380:1590–605.

8. Van Limbergen J et al. The genetics of inflammatory bowel disease. Am J Gastroenterol. 2007;102:2820–31.

9. Guo QS et al. NOD2 3020insC frameshift mutation is not associated with inflammatory bowel disease in Chinese patients of Han nationality. World J Gastroenterol. 2004;10:1069–71.

10. Scharl M, Rogler G. Inflammatory bowel disease: dysfunction of autophagy? Dig Dis. 2012;30(Suppl 3):12–9.

11. Ng SC et al. Relationship between human intestinal dendritic cells, gut microbiota, and disease activity in Crohn's disease. Inflamm Bowel Dis. 2011;17:2027–37.

12. Hart AL et al. Characteristics of intestinal dendritic cells in inflammatory bowel diseases. Gastroenterology. 2005;129:50–65.

13. Seksik P et al. Effects of light smoking consumption on the clinical course of Crohn's disease. Inflamm Bowel Dis. 2009;15:734–41.

14. Lawrance IC et al. Crohn's disease and smoking: Is it ever too late to quit? J Crohns Colitis. 2013;7:e665-71.

15. Ananthakrishnan AN et al. Long-term intake of dietary fat and risk of ulcerative colitis and Crohn's disease. Gut. 2013;doi:10.1136/gutjnl-2013-305304. [Epub ahead of print].

16. Yau Y et al. Proteomics and metabolomics in inflammatory bowel disease. J Gastroenterol Hepatol. 2013;28:1076–86.

17. Gill SR et al. Metagenomic analysis of the human distal gut microbiome. Science. 2006;312:1355–9.

18. Dyson JK, Rutter MD. Colorectal cancer in inflammatory bowel disease: what is the real magnitude of the risk? World J Gastroenterol. 2012;18:3839–48.

19. Singh S et al. Inflammatory bowel disease is associated with an increased risk of melanoma: A systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2013;doi:10.1016/j.cgh.2013.04.033. [Epub ahead of print].

20. Benitez JM et al. Role of endoscopy, cross-sectional imaging and biomarkers in Crohn's disease monitoring. Gut. 2013;62:1806–16.

21. Rosa B et al. On the usefulness of small bowel capsule endoscopy in Crohn's disease. J Crohns Colitis. 2011;5:504.

22. Dubcenco E et al. Capsule endoscopy findings in patients with established and suspected small-bowel Crohn's disease: correlation with radiologic, endoscopic, and histologic findings. Gastrointest Endosc. 2005;62:538–44.

23. Kopylov U, Seidman EG. Clinical applications of small bowel capsule endoscopy. Clin Exp Gastroenterol. 2013;6:129–37.

24. Bar-Meir S. Review article: capsule endoscopy - are all small intestinal lesions Crohn's disease? Aliment Pharmacol Ther. 2006;24(Suppl 3):19–21.

25. Schulz C et al. Double-balloon enteroscopy in the diagnosis of suspected isolated Crohn's disease of the small bowel. Dig Endosc. 2013;doi:10.1111/den.12142. [Epub ahead of print].

26. Panés J et al. Systematic review: the use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. Aliment Pharmacol Ther. 2011;34:125–45.

27. Papadia C et al. Sensitivity and specificity of magnetic resonance enterography in the clinical management of fistulizing crohn's disease. Inflamm Bowel Dis. 2013;19:1896–903.

28. Patel DR et al. Comparison of small bowel follow through and abdominal CT for detecting recurrent Crohn's disease in neoterminal ileum. Eur J Radiol. 2013;82:464–71.

29. D'Haens G et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet. 2008;371:660–7.

30. Dubinsky MC et al. Serum immune responses predict rapid disease progression among children with Crohn's disease: immune responses predict disease progression. Am J Gastroenterol. 2006;101:360–7.

31. Nunes T et al. Smoking does influence disease behaviour and impacts the need for therapy in Crohn's disease in the biologic era. Aliment Pharmacol Ther. 2013;38:752-60.

32. Zachos M et al. Enteral nutritional therapy for induction of remission in Crohn's disease. Cochrane database Syst Rev. 2007;(1):CD000542.

33. Dignass A et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. J Crohns Colitis. 2010;4:28–62.

34. Spinelli A et al. Risk of postoperative recurrence and postoperative management of Crohn's disease. World J Gastroenterol. 2011;17:3213–9.

35. Nunes T et al. Oral locally active steroids in inflammatory bowel disease. J Crohns Colitis. 2013;7:183–91.

36. Selby W et al. Two-year combination antibiotic therapy with clarithromycin, rifabutin, and clofazimine for Crohn's disease. Gastroenterology. 2007;132:2313–9.

37. Sandborn WJ et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut. 2007;56:1232–9.

38. Behm BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. Cochrane database Syst. Rev. 2008;(1):CD006893.

39. Rutgeerts P et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology. 2004;126:402–13.

40. Vermeire S et al. Effectiveness of concomitant immunosuppressive therapy in suppressing the formation of antibodies to infliximab in Crohn's disease. Gut. 2007;56:1226–31.

41. Siegel CA et al. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. Clin Gastroenterol Hepatol. 2009;7:874–81.

42. Mañosa, M et al. Fecundity, pregnancy outcomes, and breastfeeding in patients with inflammatory bowel disease: a large cohort survey. Scand J Gastroenterol. 2013;48:427–32.

43. Dignass AU et al. Management of inflammatory bowel diseases during pregnancy. Dig Dis. 2009;27:341–6.

44. Baird DD et al. Increased risk of preterm birth for women with inflammatory bowel disease. Gastroenterology. 1990;99:987–94.

45. Coelho J et al. Pregnancy outcome in patients with inflammatory bowel disease treated with thiopurines: cohort from the CESAME Study. Gut. 2011;60:198–203.

EUROPEAN CHMP SUPPORTS APPROVAL OF GILEAD SCIENCES' SOVALDI® TO TREAT HEPATITIS C

AN INVESTIGATION has been undertaken into the use of Sovaldi® (sofosbuvir 400 mg), a once-daily oral nucleotide analogue polymerase inhibitor for the treatment of chronic hepatitis C virus (HCV) infection in adults.

The European Committee for Medicinal Products for Human Use (CHMP) supports this with a positive attitude towards the Gilead Sciences, Inc.'s Marketing Authorisation Application (MAA). The CHMP favour the treatment of HCV with Sovaldi combined with other agents. If approved by the European Commission, sofosbuvir could be available in the 28 countries of the EU in the first quarter of 2014.

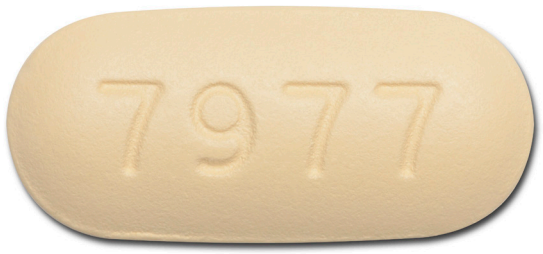
"Today's CHMP positive opinion is a positive advance for patients living with Hepatitis C in Europe. The approval of sofosbuvir means that patients with hepatitis C living in Europe are now one step closer to being able to access a medicine which may improve their chances of cure."

Mrs Tatjana Reic, President, European Liver Patients' Association

Gilead Sciences, Inc. announced the news in November, 2013. It is a biopharmaceutical company that discovers, develops, and commercialises innovative therapeutics in areas of unmet medical need. They aspire to advance the care of patients suffering life-threatening diseases.

Chronic HCV is a primary cause of liver cancer and liver transplantation in Europe and around the world. Currently, treatment of HCV involves 48 weeks of therapy with a pegylated interferon (peg-IFN)/ribavirin (RBV)-containing regimen. These are not always successful however, and include various side-effects and contraindications with other medicines.

Mrs Tatjana Reic, President of ELPA, the European Liver Patients' Association, stated: "Today's CHMP positive opinion is a positive advance for patients living with Hepatitis C in Europe. The approval of sofosbuvir means that patients with hepatitis C living in Europe are now one step closer to being able to access a medicine which may improve their chances of cure."



The MAA for sofosbuvir is mainly supported by data from four Phase III studies; NEUTRINO, FISSION, POSITRON, and FUSION in which 12 or 16 weeks of sofosbuvir-based therapy was found to be superior or non-inferior to currently available treatment options or historical controls,

based on the proportion of patients who had sustained virologic response (were HCV undetectable) 12 weeks after completing therapy (SVR12). Patients who achieve SVR12 are considered to be cured of HCV. Whilst the European Review was taking place, data from two more Phase III studies, VALENCE and PHOTON-1, were filed to the MAA. In all Phase III studies of sofosbuvir, no viral resistance to the drug was detected among patients who relapsed following completion of therapy.

Sofosbuvir was tolerated well in clinical studies in the 3,000 patients who received at least one dose in Phase II or III studies.

An expert advisory committee of the United States Food and Drug Administration (FDA) voted unanimously (15-0) in October, 2013 that the data available support the approval of sofosbuvir. The safety and the efficacy of the drug have not yet been realised.

Prof Graham Foster, Professor of Hepatology, Queen Mary, University of London, UK, mentioned: "Sofosbuvir is a very important new weapon in our fight against hepatitis C. For many patients with this infection, current treatments are unsatisfactory or ineffective and many of us are seeing more and more patients develop end-stage liver disease or liver cancer from uncontrolled hepatitis C.

"Sofosbuvir is a real breakthrough treatment that will increase the number of patients who can be treated and increase the number of patients whose infection can be controlled. We are all looking forward to this drug being made available for our patients," he added.

"Sofosbuvir is a real breakthrough treatment that will increase the number of patients who can be treated and increase the number of patients whose infection can be controlled. We are all looking forward to this drug being made available for our patients."

Prof Graham Foster,
Professor of Hepatology,
Queen Mary University, UK

A coffee a day keeps liver cancer away

DRINKING coffee could reduce the risk of hepatocellular carcinoma (HCC), a common type of liver cancer, by 40%. The risk of liver cancer can be reduced by 50% if three cups of coffee are consumed per day.

Liver cancer is the third most common cause of cancer death, and HCC accounts for more than 90% of cases worldwide. The researchers analysed the findings of 16 articles, totalling 3,153 cases, from 1996 to 2012. The last meta-analysis was undertaken in 2007, since then there has been over 900 cases of HC.

Study author, Dr Carlo La Vecchia, Department of Epidemiology, and Department of Clinical Sciences and Community Health, University of Milan, Italy, said: "Our research confirms past claims that coffee is good for your health, and particularly the liver."

She added: "The favourable effect of coffee on liver cancer might be mediated by coffee's proven prevention of diabetes, a known risk factor for this disease, or for its beneficial effect on cirrhosis and liver enzymes."

However, it is unclear whether coffee drinking in HCC is causal or not, as many patients often reduce their coffee intake. Dr La Vecchia commented: "But, in any case, such a role would be limited as compared to what is achievable through the current measures."

Three measures: a hepatitis B virus vaccination, control of hepatitis C virus transmission, and reduction in alcohol consumption, could, in principal, prevent more than 90% of cases of primary liver cancer worldwide.

"The favourable effect of coffee on liver cancer might be mediated by coffee's proven prevention of diabetes, a known risk factor for this disease, or for its beneficial effect on cirrhosis and liver enzymes."

Dr Carlo La Vecchia
University of Milan, Italy

Surgery not always the solution for GERD

ANTIREFLUX procedures (ARPs) are not always the best course of action for children suffering from gastroesophageal reflux disease (GERD), as symptoms are often found to decrease as they mature.

Infant reflux regularly occurs in babies and young children after feeding and is no cause for concern if they continue to thrive and gain weight, however if the fluid they spit out is green or yellow, contains blood, or looks like coffee grounds, it may indicate they are suffering from GERD.

"The implications of inappropriate use of ARP in infants are significant, with other studies suggesting that success rates may be lower and recurrence rates higher among these patients."

Researchers, Seattle Children's Hospital, Seattle, USA

Researchers at the Seattle Children's Hospital, USA, studied 11,621 patients who underwent ARPs and discovered that more than half were aged 6 months or under, although symptoms of GERD often resolve themselves before the infant is a year old.

It was noted that management of ARP treatment is not always consistent towards the very young, with researchers stating: "Many infants are likely never given an adequate trial of medical management.

"The implications of inappropriate use of ARP in infants are significant, with other studies suggesting that success rates may be lower and recurrence rates higher among these patients," the authors concluded.

Furthermore, researchers commented: "A standardised evaluation is not common practise." Therefore if this was developed, fewer surgeries, which could be potentially dangerous for infants, may need to take place.

Other therapies for if the condition does not naturally resolve itself have also been suggested, such as feeding and/or position changes.

The key to intestinal health - HDAC3

"There's a fundamental change in the relationship between commensal bacteria and their mammalian hosts following deletion of HDAC3 in the intestine."

Prof David Artis
Associate Professor of Microbiology, University of Pennsylvania, USA

THE ENZYME HDAC3 is believed to be crucial in maintaining good intestinal wellbeing as it has several inflammatory and metabolic roles, with research showing that those who lack HDAC3 often experience symptoms of Inflammatory Bowel Disease (IBD).

HDAC3 is an enzyme that modifies DNA and turns down genes expression, however researchers at the Perelman School of Medicine, University of Pennsylvania, USA, found that this expression was significantly reduced in intestinal tissues from those with IBD.

Dr Theresa Alenghat, lead author, Department of Microbiology, University of Pennsylvania, said: "HDAC3 in intestinal epithelial cells regulates the relationship between commensal bacteria and mammalian intestine physiology."

The research team created transgenic mice without HDAC3 in order to investigate the enzyme's effects, which led them to discover that the mice lacked Paneth cells: producers of antimicrobial peptides. Their intestines were also more porous and there were signs of chronic intestinal inflammation and IBD.

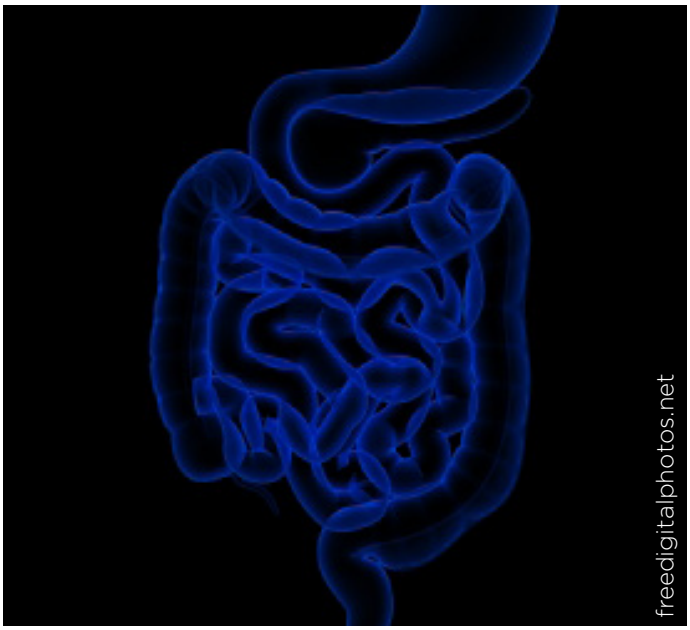
Prof David Artis, Associate Professor of Microbiology, University of Pennsylvania, stated: "There's a fundamental change in the relationship between commensal bacteria and their mammalian hosts following deletion of HDAC3 in the intestine."

The implication here, Prof Artis continued, is that "intestinal expression of HDAC3 is an essential component of how mammals regulate the relationship between commensal bacteria and normal, healthy intestinal function."

Further research on whether dysregulation of HDAC may contribute to IBD along with other diseases is currently ongoing.

"Intestinal expression of HDAC3 is an essential component of how mammals regulate the relationship between commensal bacteria and normal, healthy intestinal function."

Prof David Artis
Associate Professor of Microbiology, University of Pennsylvania, USA



Butyrate: a positive influence for IBD patients

"Regulatory T cells are important for the containment of excessive inflammatory responses as well as autoimmune disorders. Therefore, these findings could be applicable for the prevention and treatment of inflammatory bowel disease (IBD), allergy, and autoimmune disease."

Dr Hiroshi Ohno
RIKEN Center, Kanagawa, Japan

BUTYRATE, a fatty acid in the bacteria of the gut, which occurs when the bacteria digest dietary fibre, can help to reduce inflammation by influencing the immune system to produce more regulatory T cells.

These findings were observed by a research group from the RIKEN Center for Integrative Medical Sciences (IMS-RCA/), Kanagawa, Japan, who now hope butyrate may be able to treat inflammatory bowel disease (IBD) such as Crohn's Disease, along with autoimmune disorders and allergies.

The gut bacteria in those with IBD do not make butyrate and only have low levels present within their gut. Butyrate influences the production of cells that calm down the effect of other cells through reducing inflammation response. Researchers described this as 'epigenetic switching'.

It was observed that after being given a diet containing butyrate, mice with colitis had an increased number of regulatory T cells and their inflammatory symptoms improved.

The leader of the study, Dr Hiroshi Ohno from the Laboratory for Epithelial Immunobiology at the RIKEN Center, Kanagawa, Japan, noted: "Regulatory T cells are important for the containment of excessive inflammatory responses as well as autoimmune disorders. Therefore, these findings could be applicable for the prevention and treatment of IBD, allergy, and autoimmune disease."

Dr. Hiroshi Ohno advocates butyrate, because he believes it is a natural, safe, and cheap therapy. It also demonstrates the more positive role that gut microbes can play in human health.

Specialists could save the lives of bowel cancer patients

"Bowel cancer specialists are deciding whether or not a patient is suitable for liver surgery. And we're seeing liver specialists disagree with the decision in almost half of cases, meaning that some patients are denied an operation that could save their lives."

Mr Alastair Young
St James's University Hospital, Leeds, UK

BOWEL cancer patients could benefit from being assessed by liver specialists; if detected early enough, this new finding may help save the lives of many sufferers.

This study, led by Cancer Research UK, concluded that bowel cancer spreads to the liver in around half of all the 40,000 cases diagnosed every year. However in the case of liver surgery in Yorkshire, only one-fifth of patients were referred to liver specialists.

Results varied within hospitals, with one referring as many as 43% of bowel cancer patients to liver specialists, while another only 13%.

Study author and surgical registrar, Mr Alastair Young, St James's University Hospital, Leeds, UK explained: "Bowel cancer specialists are deciding whether or not a patient is suitable for liver surgery. And we're seeing liver specialists disagree with the decision in almost half of cases, meaning that some patients are denied an operation that could save their lives."

Research from St James's looks at treatment of more than 600 patients with bowel cancer which spread to the liver. One in five patients were referred to liver specialists, of these patients, three-quarters were fit for surgery. Liver specialists also disagreed with 44% of the other cases involving those bowel specialists, as they had decided the patients did not need to undergo a liver operation.

Prof Peter Johnson, Chief Clinician at Cancer Research UK, stated: "This shows how important it is for cancer specialists to collaborate when discussing treatment so all patients can benefit from their collective medical expertise."

"This shows how important it is for cancer specialists to collaborate when discussing treatment so all patients can benefit from their collective medical expertise."

Prof Peter Johnson
Chief Clinician, Cancer Research UK

Is there a link between autism and tummy troubles?

AUTISTIC children are six-to-eight times more likely to suffer from gastrointestinal (GI) upsets, compared to children who are developing normally. These GI troubles are related to behavioural problems, such as irritability, social withdrawal, and repetitive behaviour.

Lead author of the study, Ms Virginia Cheldez, Department of Public Health Sciences, University of California-Davis MIND Institute, USA, said: "Parents of children with autism have long said that their kids endure more GI problems, but little has been known about the true prevalence of these complications or their underlying causes."

The study, Childhood Autism Risks from Genetics and the Environment (CHARGE), included 1,000 children between the ages of 24 and 60 months, it is the largest and most ethnically diverse study comparing abdominal troubles in autistic children and delayed development and typical development. Moreover, it is the first study exploring the relationship between stomach and behavioural problems.

> "Our data clearly show that gastrointestinal problems are very common in children with autism."
>
> *Prof Irva Hertz-Picciotto, University of California, Davis MIND Institute, USA*

Researchers found that, compared to children developing typically, autistic children were up to eight times more likely to report food sensitivities, bloating, constipation, and diarrhoea. Moreover, GI symptoms may mean one is less likely to engage socially, an attribute associated with children who lack communication and social skills. A coping mechanism for this may be hyperactivity and repetitive behaviour.

"After years of parents raising concerns about such symptoms, the huge differences we see between parental reports on children with autism spectrum disorder versus those on children with typical development puts to rest the idea that gastrointestinal problems among children with autism spectrum disorder are just an accumulation of case reports.

"Our data clearly show that gastrointestinal problems are very common in children with autism," said Prof Irva Hertz-Picciotto, principal investigator for the CHARGE Study, a researcher affiliated with the MIND Institute.

A full GI evaluation will be beneficial for these children; the treatments could alleviate tummy troubles, and may improve behavioural problems. If there is a better understanding of GI problems this, in turn, may lead to effective autism treatments.

Is screening to detect coeliac disease the best option?

SCREENING to detect gluten intolerance, coeliac disease, in children may not always be the preferred option as the detection of the disease, and the follow-up treatment, may not improve the patients' quality of life.

Coeliac disease is an autoimmune disorder of the small intestine. However, the benefits of screening for the disease are controversial, and while there is an epidemic of the disease in Sweden, researchers investigated both the issues of screening and the disease itself in children.

"Most kids can handle the concerns of the screening examination, and thoughts about the disease may present. However, there was no consensus that the detection of disease, and treatment, results in an increased health-related quality of life," said Katrina Nordyke, a PhD student at the Department of Public Health and Clinical Medicine, Umeá University, Sweden.

"Most kids can handle the concerns of the screening examination, and thoughts about the disease may present. However, there was no consensus that the detection of disease, and treatment, results in an increased health-related quality of life."

Katrina Nordyke
Umeá University, Sweden

The children involved in the study wrote a series of short stories, first describing their feelings before they received their screening results. Their stories showed that some of them felt fear and anxiety, but they managed the screening process well. Secondly, after screening and also 1 year after diagnosis, the children answered a survey detailing their health-related quality of life. Lastly, children who received a coeliac diagnosis wrote stories at 1 year and 5 years post-screening.

Katrina Nordyke said: "5 years after diagnosis of coeliac disease, the majority of young people have learned to live with the disease, and acquired habits and strategies to cope with living with gluten-free diet. But at the same time some of these young people still doubt the benefits of having been diagnosed with coeliac disease through the screening."

Colon cancer linked with gut bacteria imbalance

"We saw more than two times the number of tumours in mice that received the cancerous community [than in mice that received a healthy gut community]. That convinced us that it is the community that is driving tumorigenesis. It's not just the microbiome, it's not just the inflammation, it's both."

Prof Patrick Schloss
University of Michigan, USA

DYSBIOSIS may drive colorectal cancer, as derived by researchers who transferred gut microbes from mice with colon tumours to germ-free mice and found it made them prone to tumours as well. The finding suggested that gut microbes may also play a role in the development of colon cancer.

The researchers of this study said: "We demonstrate, using a mouse model of inflammation-driven colon cancer, that there are dramatic, continual alterations in the microbiome during the development of tumours, which are directly responsible for tumour development." Thus, confirming how chronic gut inflammation is a known factor for developing colorectal cancer, along with eating too much red meat and drinking too much alcohol.

Prof Patrick Schloss, study author and Professor of Microbiology and Immunology, University of Michigan, USA, stated: "We saw more than two times the number of tumours in mice that received the cancerous community [than in mice that received a healthy gut community]. That convinced us that it is the community that is driving tumorigenesis. It's not just the microbiome, it's not just the inflammation, it's both."

The mice that received a microbiome from those infected with tumours had more than twice as many colon tumours than those that were given a healthy microbiome. As a result, it is subsequently being investigated which bacteria are associated with tumours.

Prof Schloss concluded: "If you can better understand what functions in the microbial community are important for protecting against tumour formation or making it worse, we can hopefully translate those results to humans to understand why people do or do not get colorectal cancer, to help develop therapeutics or dietary manipulations to reduce people's risk."

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Prof Patrick Schloss
University of Michigan, USA

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Rifaximin-α

INTERNATIONAL ABBREVIATED PRESCRIBING INFORMATION: XIFAXAN®/ TARGAXAN® 550 mg (rifaximin)
Presentation: Blister pack containing 14 film-coated, pink tablets of 550 mg rifaximin for oral administration. **Indication:** Reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥18 years of age. **Dosage and administration:** Recommended dose: 550 mg twice a day orally with a glass of water, with or without food. No specific dosing adjustment is necessary for patients with hepatic insufficiency or for the elderly. **Contraindications:** Hypersensitivity to rifaximin, any rifamycin antimicrobial agents or any of the excipients. Cases of intestinal obstruction. **Warnings and precautions:** The safety and effectiveness of XIFAXAN® for the prevention of recurrence of hepatic encephalopathy have not been established in patients under 18 years of age. *Clostridium difficile*-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including rifaximin. The potential association of rifaximin treatment with CDAD and pseudomembranous colitis (PMC) cannot be ruled out. Caution is advised in patients with impaired renal function. Concomitant administration of rifaximin with other rifamycins is not recommended. Caution should be exercised when administering XIFAXAN® to patients with severe hepatic impairment (Child-Pugh C) and in patients with MELD (Model for End-Stage Liver Disease) score >25. **Interactions:** Due to the negligible gastrointestinal absorption of orally administered rifaximin, the systemic drug interaction potential is low. *In vitro* studies have shown that rifaximin did not inhibit cytochrome P450 isozymes 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and CYP3A4 at concentrations up to 200 ng/mL (at least 10 times the clinical C_{max}). Rifaximin is not expected to inhibit these enzymes in clinical use. The effectiveness of oral oestrogenic contraceptives could decrease after rifaximin administration. Additional contraceptive precautions are recommended, in particular if the oestrogen content is less than 50 µg. **Pregnancy and lactation:** Nonclinical studies of placental transfer of rifaximin/metabolites have not been conducted. There was no evidence of teratogenicity in pregnant rats or rabbits treated with rifaximin during the period of organogenesis. It is unknown whether rifaximin/metabolites are excreted in human milk. A risk to the child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from rifaximin therapy. Use of rifaximin during pregnancy is not recommended. **Undesirable effects:** The adverse effects identified from the pivotal clinical trial most likely to be associated with rifaximin treatment (incidence ≥10%) are: nausea, dizziness, ascites, oedema peripheral. The following adverse reactions have been identified during post approval use of rifaximin. Common (≥1/100 to <1/10): Depression, dizziness, headache, dyspnoea, abdominal pain upper, abdominal distension, diarrhoea, nausea, vomiting, ascites, rashes, pruritus, muscle spasms, arthralgia. Prescribers should consult country approved prescribing information for further information in relation to undesirable effects. **Overdose:** No case of overdose has been reported. In patients with normal bacterial flora, rifaximin in dosages of up to 2,400 mg/day for 7 days did not result in any relevant clinical symptoms related to the high dosage. In case of accidental overdosage, symptomatic treatments and supportive care are suggested. **Price and pack sizes:** PVC-PE-PVDC/Aluminium foil blisters in cartons of 28 or 56 tablets. Contact local distributor for price. **Legal category:** POM. **Prescribing information:** Medicinal product subject to medical prescription. **Marketing authorisation holder:** Norgine Pharmaceuticals Ltd. Norgine House, Widewater Place, Moorhall Road, Harefield, Middlesex UB9 6NS, UK. **Product licence number:** PL20011/0020.

ATC code: A07AA11. **Date International Prescribing Information prepared:** 4 April 2013. **Company reference:** INT/XIF/0413/0187.

XIFAXAN® has varying availability and licensing internationally. Before prescribing, consult your country approved prescribing information, available from your local distributor or Norgine Ltd.

Adverse events should be reported to your regulatory agency. Adverse events should also be reported to your local distributor or Norgine Limited, Norgine House, Moorhall Road, Harefield, Uxbridge, Middlesex UB9 6NS, United Kingdom. Email: globalmedinfo@norgine.com

References: 1. Bass, N.M., *et al.* N Engl J Med, 2010; 362(12): 1071-81. 2. Sanyal, A., *et al.* Aliment Pharmacol Ther, 2011; 34(8): 853-61. 3. Norgine data on file. 4. XIFAXAN® 550 Summary of Product Characteristics, 2012.

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

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NORGINE

Clinical Tutoring-Performance of Endoscopic Submucosal Dissection (ESD)

3rd-6th February 2014 and 9th-11th April 2014

Salzburg, Austria

This course aims to spread the knowledge of ESD technique for experienced endoscopists by individual instruction from international experts. Over the 3 days, you will expect to find an analysis of video recordings, instruction on prevention and management of complications, and training of technically challenging ESD procedures will also be provided.

16th Düsseldorf International Endoscopy Symposium

6th-8th February 2014

Düsseldorf, Germany

This conference will feature live demonstrations, state of the art lectures, mini and satellite conferences, and updates on research and new technologies, including: molecular imaging, biodegradable and drug-eluting stents. Other main topics include the role of endoscopy in acute pancreatitis and the benefits of cholangioscopy's advanced techniques.

9th Congress of the European Crohn's and Colitis Organisation

20th-22nd February 2014

Copenhagen, Denmark

This Congress aims to deliver the most recent scientific information on adult and childhood gastroenterology, endoscopy, imaging, and surgery. There will be eight sessions, structured around basic science, translational medicine, clinical practice, and patient care. There will also be educational activities including the 12th Inflammatory Bowel Disease (IBD) Intensive Advanced Course for Junior Gastroenterologists.

10th Annual Gastroenterology Conference

3rd-4th April 2014

Sarajevo, Bosnia and Herzegovina

This Conference aims to improve endoscopy techniques, equipment, and training, while also discussing topics such as acid related diseases, nutrition, gastrointestinal oncology, chronic hepatitis, irritable bowel syndrome (IBS), and IBD.

Endo Live Roma 2014

22nd-23rd May 2014

Rome, Italy

This event aims to encourage a multidisciplinary approach among gastroenterologists, endoscopists, and surgeons. This event will feature live demonstrations, lectures, and symposiums on the most current endoscopic techniques and procedures in the diagnosis and treatment of digestive diseases.

32nd GEEW - Gastroenterology and Endotherapy European Workshop

23rd-25th June 2014

Brussels, Belgium

This workshop aims to evaluate established and recent endoscopy techniques, assessing their clinical unity in a multidisciplinary setting. Topics which will be discussed include new diagnostic imaging in upper and lower gastrointestinal endoscopy, endoluminal transoral surgery for morbid obesity, and the latest technologies for haemostasis, bleeding ulcers and varices.

ESGE (European Society of Gastrointestinal Endoscopy) Live Demonstration

12th-13th September 2014

Prague, Czech Republic

This event aims to deliver the basic principles and latest news in advanced endoscopic techniques, whilst providing hands-on training via animal models on various options of ablative techniques and tissue closure. Participants are encouraged to share their knowledge through interactive sessions and state-of-the-art lectures. There will also be an emphasis on new technologies such as biliary and pancreatic endotherapy, and topical treatment of GI bleeding.

UEG (United European Gastroenterology) Week Vienna 2014

18th-22nd October 2014

Vienna, Austria

UEG week aims to cover all aspects of gastroenterology ranging from basic science to clinical practice guidelines. The meeting will focus on areas where substantial progress has been made, with a particular focus placed on digestive oncology. The meeting will comprise of live endoscopy sessions, and the 2-day 'Today's science; tomorrow's medicine' initiative.