EMJ EUROPEAN MEDICAL JOURNAL

GASTROENTEROLOGY

ISSN 2054-6203 — Vol 7.1 • December 2018 • europeanmedical-journal.com

INSIDE

Review of

UEG WEEK 2018

Vienna, Austria

Contents

"On behalf of the EMJ team, I am proud to welcome you to the seventh edition of EMJ Gastroenterology, one of EMJ's most well-established and renowned eJournals."

Spencer Gore, CEO

Editorial Board

VIEW IN FULL ←

Aims and Scope

The European Medical Journal (EMJ) is an online only, peer-reviewed, open access general journal, targeted towards readers in the medical sciences. We aim to make all our articles accessible to readers from any medical discipline.

EMJ allows healthcare professionals to stay abreast of key advances and opinions across Europe.

EMJ aims to support healthcare professionals in continuously developing their knowledge, effectiveness, and productivity. The editorial policy is designed to encourage discussion among this peer group.

EMJ is published quarterly and comprises review articles, case reports, practice guides, theoretical discussions, and original research.

EMJ also publishes 16 therapeutic area journals, which provide concise coverage of salient developments at the leading European congresses. These are published annually, approximately 6 weeks after the relevant congress. Further details can be found on our website: www.europeanmedical-journal.com

Editorial Expertise

EMJ is supported by various levels of expertise:

- Guidance from an Editorial Board consisting of leading authorities from a wide variety of disciplines.
- Invited contributors are recognised authorities from their respective fields.
- Peer review, which is conducted by EMJ's Peer Review Panel as well as other experts appointed due to their knowledge of a specific topic.
- An experienced team of editors and technical editors.

Peer Review

On submission, all articles are assessed by the editorial team to determine their suitability for the journal and appropriateness for peer review.

Editorial staff, following consultation with either a member of the Editorial Board or the author(s) if necessary, identify three appropriate reviewers, who are selected based on their specialist knowledge in the relevant area.

All peer review is double blind.

Following review, papers are either accepted without modification, returned to the author(s) to incorporate required changes, or rejected.

Editorial staff have final discretion over any proposed amendments.

Submissions

We welcome contributions from professionals, consultants, academics, and industry leaders on relevant and topical subjects.

We seek papers with the most current, interesting, and relevant information in each therapeutic area and accept original research, review articles, case reports, and features.

We are always keen to hear from healthcare professionals wishing to discuss potential submissions, please email: editorial.assistant@emjreviews.com

To submit a paper, use our online submission site: www.editorialmanager.com/e-m-j

Submission details can be found through our website: www.europeanmedical-journal.com/contributors/authors

Reprints

All articles included in EMJ are available as reprints (minimum order 1,000). Please contact hello@europeanmedical-journal.com if you would like to order reprints.

Distribution and Readership

EMJ is distributed through controlled circulation to healthcare professionals in the relevant fields across Europe.

Indexing and Availability

EMJ is indexed on DOAJ, the Royal Society of Medicine, and Google Scholar®; selected articles are indexed in PubMed Central®.

EMJ is available through the websites of our leading partners and collaborating societies.

EMJ journals are all available via our website: www.europeanmedical-journal.com

Open Access

Congress Notice

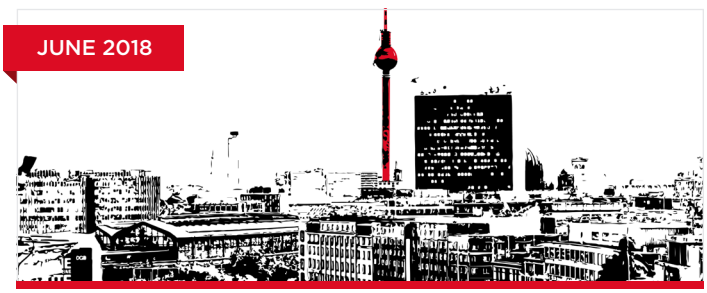
Staff members attend medical congresses as reporters when required.

This Publication

European Medical Journal Gastroenterology is published once a year. For subscription details please visit: www.europeanmedical-journal.com

Front cover and contents photograph: Vienna, Austria, home of the UEG Week 2018. © sorincolac / 123rf.com

EMJ Gastroenterol.



European Medical Journal 3.2

EMJ 3.2 has entered the building! This truly multidisciplinary eJournal returns for its 10th issue and its second of 2018. *EMJ 3.2* includes a plethora of high-quality peer-reviewed...

VIEW ALL JOURNALS ←

Welcome

On behalf of the EMJ team, I am proud to welcome you to the seventh edition of *EMJ Gastroenterology,* one of EMJ's most well-established and renowned eJournals. In modern-day healthcare, gastroenterological conditions are commonly seen and significantly impact care and quality of life of patients from various fields of medicine. Therefore, we are pleased to be able to share with you *EMJ Gastroenterology 7.1*, providing you with key updates from this fast-paced and important discipline.

Once again, the EMJ reporting team attended the United European Gastroenterology (UEG) Week, which this year took place in October in the picturesque city of Vienna, Austria. In order to create our independent review of the event for your reading pleasure, we immersed ourselves in Europe's gastroenterological advances from 2018. Some of the key developments were focussed on screening for young-onset colorectal cancer, the risks associated with oesophageal cancer, and cannabis oil as a novel treatment for Crohn's disease. In addition, with >2,000 abstracts presented during UEG Week, we are pleased to bring you a hand-picked selection of abstract summaries penned by the authors themselves. If you missed this fantastic event or would simply like to refresh your memory of the highlights, turn to the Congress Review section of this eJournal.

Also captured within the pages of *EMJ Gastroenterology 7.1* are significant developments in the understanding of a variety of inflammatory disorders involving the gastroenterological system, which can be found throughout the peer-reviewed articles included within. We have the pleasure of working with leading experts from the field on a daily basis and are proud to share their work with you. The Editor's Pick for this issue is a contribution by Menezes-Garcia et al. on the undesired development of mucositis during chemotherapy. Reviewing the inflammatory mechanisms behind the toxic effect of this common cancer treatment, the authors explore mucositis prevention and therapeutics in a paper that will greatly enhance understanding and oncology patient care. Other articles of interest include reviews of malignant colorectal polyps and radiation bowel disease, as well as an insightful paper by Mikhail et al. on gastroenterological causes of non-cardiac chest pain.

This edition of *EMJ Gastroenterology* covers a wide spectrum of disorders, from common conditions to more unusual treatment outcomes, and will impact clinical and research practices alike. We hope that not only gastroenterologists but medical professionals from all disciplines will enjoy and learn from the exciting content. Don't forget, if you would like to join the panel of *EMJ Gastroenterology* contributors for next year's edition, be sure to get in touch!

Kind regards,

Spencer Gore

Chief Executive Officer, European Medical Group

Foreword

Dear colleagues and friends of gastroenterology,

It is my great privilege to present you with the 2018 edition of *EMJ Gastroenterology* and invite you to read on and update yourself with the latest happenings from the gastroenterological field.

Nowadays, digestive diseases require multidisciplinary treatment. The United European Gastroenterology (UEG) Week provides an extraordinary opportunity for both clinicians (gastroenterologists, gastrointestinal surgeons, and oncologists) and basic researchers to come together from all parts of the world to discuss latest advances in the field. Attending UEG Week 2018 was a tremendous experience and reading this eJournal's Congress Review section channels the occasion's passion and electric atmosphere. Inside this section, you will find highlights of some of the hottest news stories shared at UEG Week, including some top abstract prizes like use of early surgery for the management of chronic pancreatitis and results of a first phase randomised controlled study comparing laparoscopic versus open surgery in pancreatoduodenectomy. As a surgeon, I am proud to see more surgeons attending UEG Week every year, presenting their excellent results.

Inside this eJournal, my colleagues on the *EMJ Gastroenterology* Editorial Board provide insights regarding who and what inspired them at the start of their gastroenterological journey, their top pieces of advice, and their thoughts on the field's future directions. You can also read how social media usage has changed the discipline, how to develop an effective training course, and the differences between the European Union (EU) and the USA regarding pharmaceutical guidelines.

The Editor's Pick for this issue, selected by EMJ Editor Samantha Warne, is a wonderful paper by Menezes-Garcia et al. that reviews the role of inflammatory mediators and potential therapeutic targets for treating chemotherapy-associated mucositis. Further research is undeniably required to advance the treatment of this condition and this thorough review presents an important foundation from which to launch future studies.

I would like to take this opportunity to extend my thanks to all of you who contributed to this journal. Furthermore, I would also like to urge you to contribute to next year's edition and play a part in shaping *EMJ Gastroenterology*. If you enjoyed reading the journal, make sure you spread the word to your colleagues and peers.

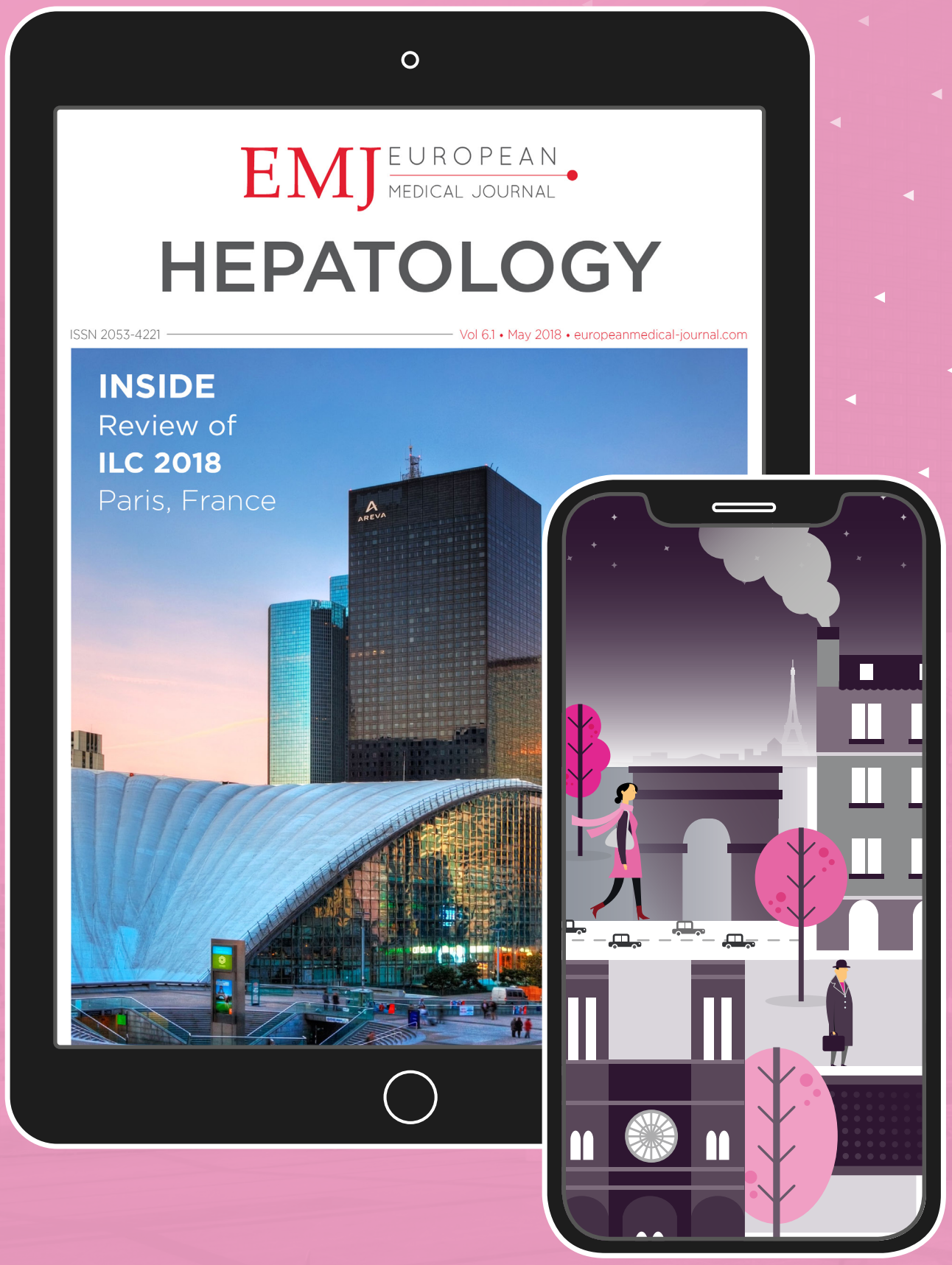
Lastly, I consider it an honor to be the Editor-in-Chief of *EMJ Gastroenterology*, and, with my team of motivated and qualified editors, look forward to making it a marquee journal in the field of gastroenterology.

With best wishes,

Dr Sorin T. Barbu

"Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj, Romania

Available now.



Inside this eJournal:

Congress Review

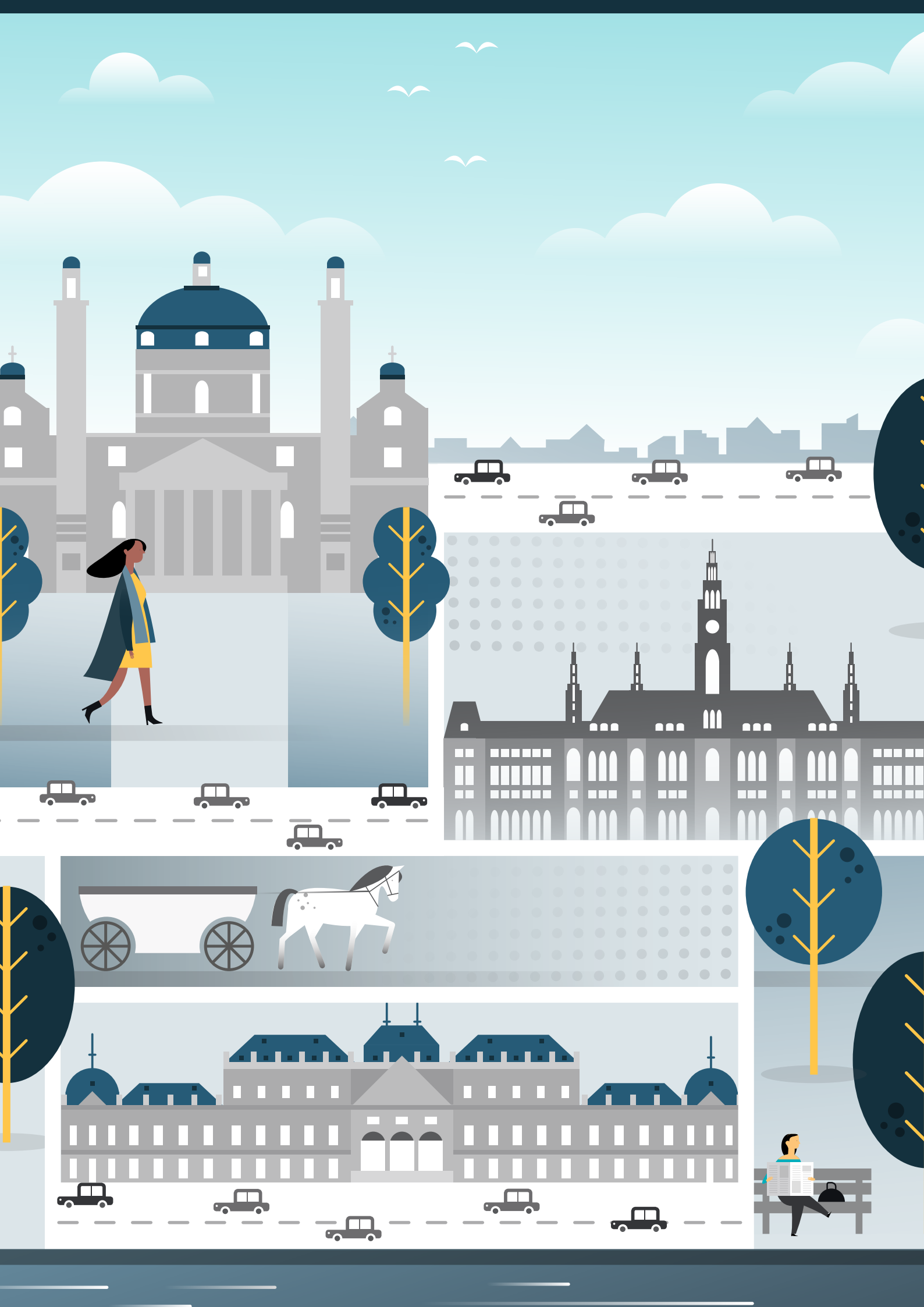
Abstract Reviews

Articles

And even more...

EMJ Hepatology 6.1 provides influential articles, presentations of scientific research and clinical practice, and an in-depth review of ILC 2018.

Subscribe for free.



Congress Review

Review of the 26th United European Gastroenterology (UEG) Week

Location: Vienna, Austria – Austria Center Vienna

Date: 20.10.18–24.10.18

Citation: EMJ Gastroenterol. 2018;7[1]:12-27. Congress Review.

"UEG Week provides a fantastic opportunity for clinicians and researchers to come together from all corners of the world to discuss advances in digestive health," Prof Herbert Tilg, Chair of the UEG Scientific Committee, declared proudly, speaking at UEG Week 2018. He went on to extoll the virtues of the event and explained that "the high volume of submissions, coupled with the first-class standard of abstracts, confirms that UEG Week is the most important forum to present gastrointestinal research."

A select team from EMJ were privileged to travel from the UK to Vienna for this occasion. Rather than to marvel at the splendour of Vienna's imperial palaces or delight in the skill of the riders at the Spanish Riding School, we arrived in Austria's capital to immerse ourselves in Europe's gastroenterological capital: UEG Week. We are now delighted to be able to present to you all of the headline news disseminated at the event within the pages of this Congress Review. Some of this news included results from the UNIFI Phase III trial into ustekinumab as an induction therapy for moderate-to-severely active ulcerative colitis, a comparison between laparoscopic ileocaecal resection and infliximab for the treatment of immunomodulator-refractory Crohn's disease, and research from the USA into the risk factors for colorectal cancer in those aged 20–49 years.

A snapshot of the event by the numbers gives some indication of its magnitude:

- Attendees came from around the globe, with 114 nations represented.
- Previous attendance records were surpassed, with 12,600 travelling to Vienna.
- 3,705 abstracts were submitted, with 2,214 of them accepted.
- 62 abstract presentation prizes were awarded.
- There were 194 scientific sessions.
- The number of lectures delivered totalled 1,129.

- The exhibition space spanned a vast 5,084 m^2, which was larger than the 4,957 m^2 at UEG Week 2017.
- There were 148 exhibitors and sponsors at the event. You can find further details of those present in our Buyer's Guide.

However, numbers alone are insufficient to demonstrate the full scale of this scientific gathering. For one thing, it was not only those physically present in Vienna who were able to share in this year's UEG Week. The congress organisers had worked hard behind the scenes to ensure a significant online presence, further extending the event's global following. This endeavour to make UEG Week even more widely accessible saw 113 sessions being streamed live over the internet. To complement this, viewers were able to use the mobile app to ask questions of the presenters in real time. The EMJ team saw this facility in full effect at a session that took place as part of the Young GI Network; the details of this highly topical discussion on balancing work with your personal life, and whether it is necessary to make sacrifices, are explored in our Congress Review. With >3,000 viewers tuning into the streamed sessions, the efforts of the organisers certainly paid off. Furthermore, the UEG Week social media accounts saw 1,481 posts over the course of the meeting, highlighting the increasing relevance of interacting across multiple channels. UEG Week's virtual presence was not only in real time; of the 1,129 lectures given, an impressive 571 were recorded for the benefit of those unable to attend the event.

Prof Tilig extended his gratitude to all those who played a part in UEG Week: "Finally, I would like to pass on a huge thank you to everyone that attended the congress, including the passionate speakers, the engaged delegates, and the enthusiastic young gastroenterologists." We here at EMJ would also like to extend our thanks to every attendee: all of you combined to make UEG 2018 a thoroughly enjoyable and memorable event. Next year will see UEG Week return to Barcelona, Spain and we hope to have the pleasure of seeing you there as well.

"Finally, I would like to pass on a huge thank you to everyone that attended the congress, including the passionate speakers, the engaged delegates, and the enthusiastic young gastroenterologists."

More Screening Required for Young-Onset Colorectal Cancer

COLORECTAL cancer cases in young European adults are becoming more common, according to an analysis of incidence rates across the continent, presented for the first time at UEG Week 2018. Reported in a UEG Week press release dated 23rd October 2018, this upward trend in the number of colorectal cancer cases suggests that more widely available screening programmes are necessary across Europe for young people.

The investigation involved analysis of data on the incidence of colorectal cancer in adults aged 20–39 years from 20 European national cancer registries, including those of Belgium, Germany, Italy, France, and the UK. While investigations of this type have been performed in North American populations, the researchers noted that, until now, the information on colorectal cancer incidence in young people in Europe has been limited.

"Increased awareness and further research to elucidate causes for this trend are needed and may help to set up screening strategies to prevent and detect these cancers at an early and curable stage."

After analysing the trends in incidence rates, the number of cases of colon cancer was shown to increase by 2.2% (95% confidence interval [CI]: 1.4–3.0) per year from 1990–2010 and by 7.3% (95% CI: 2.3–12.5) per year from 2010–2016 in men aged 20–39 years, whereas in women in the same age range, the incidence rate increased by 1.5% (95% CI: 0.4–2.7) per year from 1990–2008 and by 8.9% (95% CI: 4.8–13.2) per year from 2008–2016. A similar increased incidence rate was observed for rectal cancer: in men, rates decreased by 3.9% (95% CI:-7.1– -0.7) from 1990–1997, and increased 1.6% (95% CI: 0.8–2.3) per year from 1997–2016; in women the increase per year in 1990–1996 was 8.3% (95% CI: 4.7–12.0), but this stabilised in the years 1996–2016.). Since the malignancy is traditionally considered to affect people aged >50 years, with incidence rates higher in men than women, the research team noted that the finding that colorectal cancer is increasing in the young is worrying, particularly because young-onset cases are often more aggressive and advanced.

Hypothesising that the observed upward trend may be related to risk factors such as obesity, poor diet, and increasingly sedentary lifestyles, study presenter Dr Fanny Vuik, Department of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, Netherlands, commented: "Increased awareness and further research to elucidate causes for this trend are needed and may help to set up screening strategies to prevent and detect these cancers at an early and curable stage." Reductions in the incidence and mortality rates of colorectal cancer have been shown to result from effective screening strategies; however,

many European screening programmes are only available for people aged >50 years. Therefore, with colorectal cancer being the second most common cancer in Europe, screening adults at a younger age who may be at a high risk is essential to optimise patient outcomes and ensure an early diagnosis.

Oesophageal Cancer Risk Linked to Oesophageal Microbiota

UNIQUE microbe signatures have been found to be linked to oesophageal cancer, according to results presented in a UEG Week press release dated 23rd October 2018. It is hoped that the identification of these oesophagus microbe signatures will aid in both the diagnosis and management of oesophageal cancer.

To assess whether there is a relationship between the microbiota of the oesophagus and oesophageal cancer, researchers obtained biopsy samples from 6 newly diagnosed oesophageal cancer patients, 10 patients with Barrett's oesophagus, and 10 controls that were analysed for microbiota comparison. When the biopsies were analysed, higher levels of bacterial diversity were reported in those taken from patients with cancer compared with controls. It was identified that there was an abundance of Bacteroidetes and lower levels of Firmicutes in oesophageal cancer patients compared with controls. Comparing oesophageal cancer patient results with Barrett's oesophagus patients and controls, there were lower levels of *Streptococcus* and higher levels of *Veillonella*, *Porphyromonas*, and *Prevotella*.

Oesophageal cancer is the eighth most common cancer worldwide and, coupled with the fact that most people only present with established disease and mortality rates are high, there is a profound need to identify a way of screening for those most likely to develop the disease and to develop alternative treatments to best tackle the disease. Well-known risk factors associated with oesophageal cancer include obesity, smoking, low fruit and vegetable intake, and alcohol consumption; now, this researcher suggests that microbiota can also be added to this list.

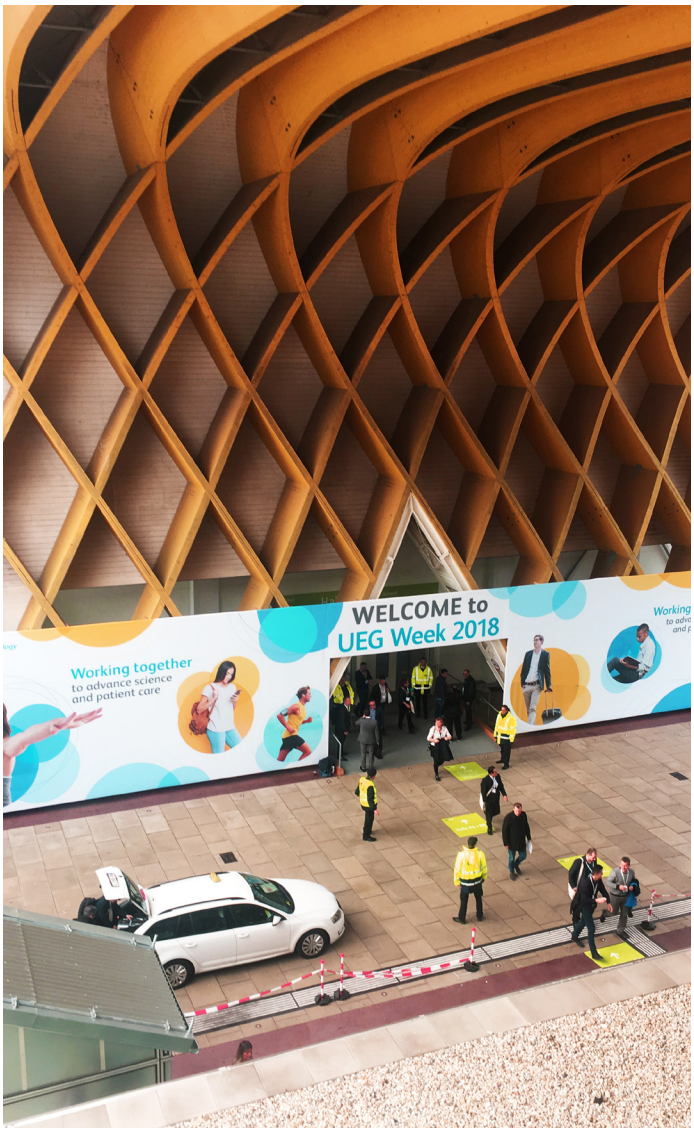
"If these findings are confirmed in our further analyses, it may be possible to imagine innovative diagnostic and therapeutic tools to help us manage this condition more successfully."

Dr Loris Riccardo Lopetuso, lead researcher, Catholic University of Rome, Rome, Italy, commented on the importance of these findings: "These results indicate that there is a unique microbial signature for oesophageal cancer that might represent a risk factor for this condition." Dr Lopetuso also spoke of the future applications for this research: "If these findings are confirmed in our further analyses, it may be possible to imagine innovative diagnostic and therapeutic tools to help us manage this condition more successfully."

Cannabis Oil and Crohn's Disease

CANNABIS OIL has been demonstrated to result in the improvement of symptoms in patients with Crohn's disease and additionally lead to an improvement in the quality of life of these patients. The results of this study were discussed in a UEG Week press release dated 22nd October 2018.

Cannabis has been used in the treatment of a number of medical conditions for centuries. It is also utilised for symptomatic relief by many patients with Crohn's disease. The researchers conducting this study set out to examine whether the improvement in symptom relief was as a result of cannabis alleviating gut inflammation.



The researchers enrolled 46 patients with moderately severe Crohn's disease. These patients were randomised to one of two treatment arms: one arm received placebo and the other arm received cannabis oil that contained 15% cannabidiol and 4% tetrahydrocannabinol. The treatment period was 8 weeks. Prior to treatment beginning, the symptom severity and quality of life of the participants were measured, as well as gut inflammation. These measurements were also taken after the treatment course.

"...to our surprise, we saw no statistically significant improvements in endoscopic scores or in the inflammatory markers we measured in the cannabis oil group compared with the placebo group."

After the 8-week treatment course, 35% of the patients in the placebo arm met the criteria for clinical remission compared with 65% of patients in the cannabis oil arm. Furthermore, those in the cannabis oil group demonstrated a significant improvement in quality of life in comparison to those in the placebo group. However, the authors were surprised by one of their findings. "We have previously demonstrated that cannabis can produce measurable improvements in Crohn's disease symptoms, but, to our surprise, we saw no statistically significant improvements in endoscopic scores or in the inflammatory markers we measured in the cannabis oil group compared with the placebo group," explained the study's lead researcher, Dr Timna Naftali, Tel Aviv University, Tel Aviv, Israel.

Bearing this finding in mind, the researchers' next steps are to study in more detail whether the endocannabinoid system is a potential treatment target for Crohn's disease and other gastrointestinal diseases. However, Dr Naftali explained that: "For now [...] we can only consider medicinal cannabis as an alternative or additional intervention that provides temporary symptom relief for some people with Crohn's disease."

Link Between Black Death and Crohn's Disease Revealed

CROHN'S disease occurrence across Europe has been linked to overcoming devastating plague outbreaks during the middle ages by new research into the genetic origins of the inflammatory disease revealed at UEG Week 2018 and reported in a UEG Week press release dated 22nd October 2018.

Inflammatory bowel disease, comprising ulcerative colitis and Crohn's disease, affects roughly 3 million individuals in Europe and costs healthcare systems across the continent >€5 billion annually. Although not fully understood, there is strong evidence to suggest that genetic factors play a role in the pathogenesis of inflammatory bowel disease, and, therefore, the researchers focussed their attention on *NOD2*, a gene known to play an important role in the immune system and mutations of which are associated with Crohn's disease.

"This research goes some way to explaining the genetic origins of Crohn's and we hope it will enable us to better understand the disease, and how to treat it, in the future."

Previous investigations have shown that genetic variation of *NOD2* was also involved in the mechanism of resistance against the causal organism responsible for millions of European deaths due to the Black Death during the 14th century. Therefore, by studying historical data, the researchers concluded that the prevalence Crohn's disease-associated *NOD2* mutations correlates with intensity of plague outbreaks, which may help to explain the modern-day incidence rates of Crohn's disease in Europe.

"Considering the potential severity of Crohn's disease when untreated, it is unlikely that is was a frequent disease before the 20th century. As healthcare systems have developed and care for Crohn's disease patients has improved, more and more people are living with the disease," elucidated researcher Prof Jean-Pierre Hugot, Paediatric Digestive and Respiratory Diseases Department, Robert Debré Hospital, Paris, France. "This research goes some way to explaining the genetic origins of Crohn's and we hope it will enable us to better understand the disease, and how to treat it, in the future," he added.

Monitoring Microplastics: The Story Continues

PLASTICS are ubiquitous with modern society, polluting the world's oceans, seas, and rivers to

an extent that, even now, is only just becoming fully understood. The effect this pollution may be having on the human gastrointestinal tract has been of growing concern for some time in the gastroenterological community and the results of a first of its kind study, reported in a UEG Week press release dated 23rd October 2018, have identified the presence of microplastics in human stool samples. The results are set to add further fuel to the fire demanding a change to the current use, manufacture, and disposal of plastics.

Eight individuals were included in the study, recruited from Finland, Austria, Poland, Italy, Japan, the Netherlands, Russia, and the UK. Participants were asked to keep a food diary for the week prior to stool sampling, and review of the food diary and the stool sample highlighted that all the participants were exposed to plastics through the consumption of plastic wrapped food and the use of plastic drinks bottles.

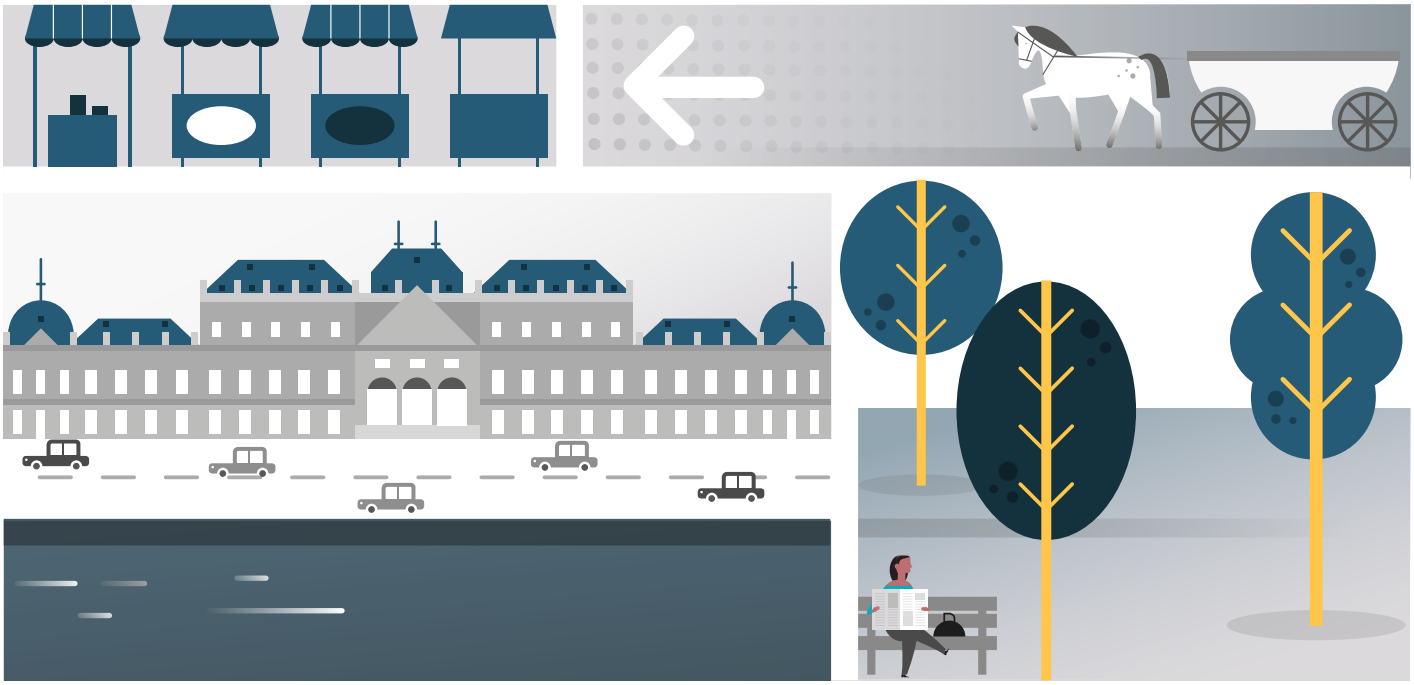
"Now that we have the first evidence for the microplastics inside humans, we need further research to understand what this means for human health."

Analysis of the stool samples, conducted at the Environment Agency Austria (UBA), showed that per 10 g of stool sample 20 microplastic particles were identified on average. Up to nine different microplastics, sized between 50 and 500 µm, were identified in the samples; polypropylene and polyethylene terephthalate were the most common microplastics.

The study is relatively small, encompassing only eight individuals, yet it raises an important point about the pervasiveness of microplastics. Study lead Dr Philipp Schwabl, Medical University of Vienna, Vienna, Austria, concluded: "While the highest concentrations in animal studies have been found in the gut, the smallest microplastics particles are capable of entering the blood stream, lymphatic system, and may even reach the liver. Now that we have the first evidence for the microplastics inside humans, we need further research to understand what this means for human health."

The Best of the Best: Top 5 Abstracts from UEG Week 2018

As ever, the annual UEG Week provided a platform for the most pivotal trials, studies, and investigations conducted over the last year to be presented to the members of the gastroenterological community. With >2,000 abstracts presented, UEG Week 2018 proved to be a record-breaking year. Among the thousands of research teams presenting their results across the 5-day event, five were singled out and presented with awards for their work.




www.acv

This year, the awards were split between researchers from the Netherlands, France, Germany, Switzerland, and the USA.

The Use of Early Surgery for Obstructive Chronic Pancreatitis Management

In the first of three award-winning studies investigating the pancreas, Dr Marinus Kempeneers and the research team behind the ESCAPE trial were awarded for their work. The team compared the effect of early surgery on the pain chronic pancreatitis patients experienced in comparison with the current standard optimised medical therapy. Overall, 88 chronic pancreatitis patients, with a ≥5 mm dilated pancreatic duct, continuous or intermittent severe pain, and previous use of strong opioids for <2 months or weak opioids for <6 months, were randomised in a 1:1 ratio to receive either early surgery or medical therapy. During the 18-month follow-up, the research identified that early surgery gave rise to a significantly lower Izbicki pain score than their optimised medical therapy counterparts (36±24 compared to 47±24; p<0.001).

The improved patient pain experience in combination with a reduced overall cost associated with early surgery (€17,522 compared with €22,366) makes early surgery a very attractive option for the management of obstructive chronic pancreatitis.

Open versus laparoscopic surgery

Continuing the theme of pancreatic surgery, the research team from the Dutch Pancreatic Cancer Group, Amsterdam, the Netherlands, investigated whether open or laparoscopic surgery gave rise to a faster time to functional recovery.

"We think that further research should focus on safety outcomes and volume thresholds for laparoscopic pancreatoduodenectomy."

Patients were randomised in a 1:1 ratio to receive laparoscopic or open surgery and were blinded to the procedure used via large dressings visually obscuring the surgical site. Laparoscopic surgery was shown to improve time to functional recovery (10 days versus 8 days for open versus laparoscopic surgery, respectively; p=0.80). However, the study was stopped early after only 99 patients had undergone the surgery, as 10% of the laparoscopic surgery cohort died due to complications (two from intraoperative damage; two from postoperative haemorrhage; and 1 from postoperative fistula) compared to only one patient in the open surgery group, as a result of haemorrhage.

Discussing the results, Dr Jony von Hilst highlighted the concerning safety aspects of the procedure: "We think that further research should focus on safety outcomes and volume thresholds for laparoscopic pancreatoduodenectomy."

Gene Expression Analysis in Inflammatory Bowel Disease

Investigators from France, Spain, Germany, and the USA collaborated to further explore the genes involved in two major inflammatory bowel diseases. They performed the first integrated gene expression analysis of >1,500 samples obtained through intestinal biopsy of patients with Crohn's diseases, ulcerative colitis, and controls.

Combining the data from six major heterogeneous studies, obtained through microarray and RNA sequencing techniques, analysis of gene expression identified a number of disease and region-specific gene clusters, including the REG genes that had a prominent effect in colonic diseases. Comparison of ulcerative colitis with ileal and colonic Crohn's diseases samples highlighted cluster of shared inflammatory genes, including *DUOX2*, *MMP1*, and *MMP3*, present in all three disease subtypes.

Dr Kevin Perez, who presented the study acknowledged the variation in sample composition was a limitation of the study, but future single cell studies will soon provide better data.

Promoting the Survival of T Helper Cells: NLRP6

"We propose that naïve T cells start to express NLRP6 upon differentiation of Th1 cells and this prevents apoptosis. We therefore suggest that NLRP6 promotes the survival of CD4 T cells," explained Dr Jan Hendrik Niess, University of Basel, Basel, Switzerland after the completion of multiple *in vitro* studies examining the effect of NLRP6 on the differentiation of T cell.

"We propose that naïve T cells start to express NLRP6 upon differentiation of Th1 cells and this prevents apoptosis. We therefore suggest that NLRP6 promotes the survival of CD4 T cells."

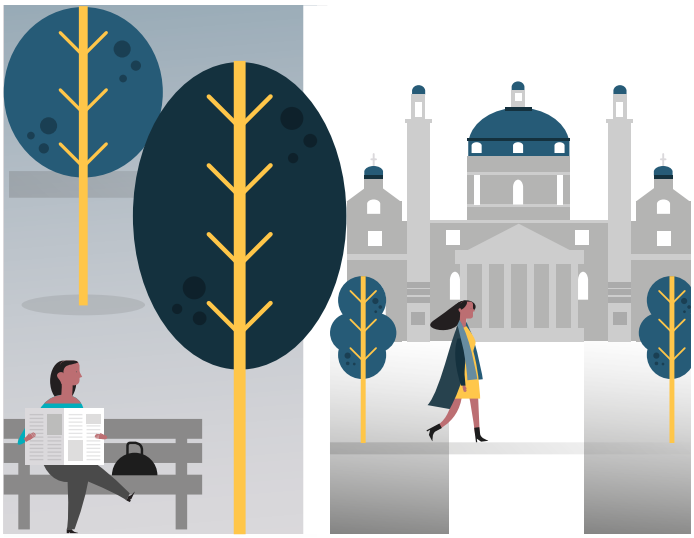
Using differentiated T cells and T cells after the co-transfer of wild-type and NLRP6-deficient cells on RAG hosts, the researchers discovered that NLRP6 deficiency did not impact upon T cell proliferation or development in mice. Additionally, the protein is not expressed by naïve CD4 and CD8 positive cells, B cells and bone marrow-derived macrophages, but is expressed by Th1 cells.

However, analysis of apoptosis markers, including TNF-α levels and IFNγ signalling, indicated that cell death is accelerated in NLRP6-deficient cells; this hypothesis was confirmed through Annexin V+ staining, highlighting the importance of the protein to the innate immune response.

Early Biliary Decompression Versus Conservative Treatment

In the last of three award-winning studies investigating pancreatic surgeries, the Dutch Pancreatic Study Group presented data that analysed the effect of early biliary decompression in comparison with conservative treatment in 232 patients with severe acute biliary pancreatitis.

The composite primary endpoint of death or major complications during the 6-month study period was observed in 45 of the 117 patients in the early biliary decompression compared with 50 of the 133 conservatively treated patients (p=0.37). The study showed that there was no statistically significant difference between the two study arms.



Dr Nicolien Schepers, who presented the award-winning data on behalf of the Dutch Pancreatic Study Group concluded: "In patients with predicted severe acute biliary pancreatitis without cholangitis, the APEC trial did not show the superiority of early ERC (endoscopic retrograde cholangiography) with sphincterotomy as compared with conservative treatment."

Conclusion

This year proved to be a landmark year for gastroenterological research, with the Dutch investigative teams leading the way for pancreatic research. An additional selection of some of the other top studies presented at UEG Week 2018 can be found within the Abstract Reviews section of the eJournal.

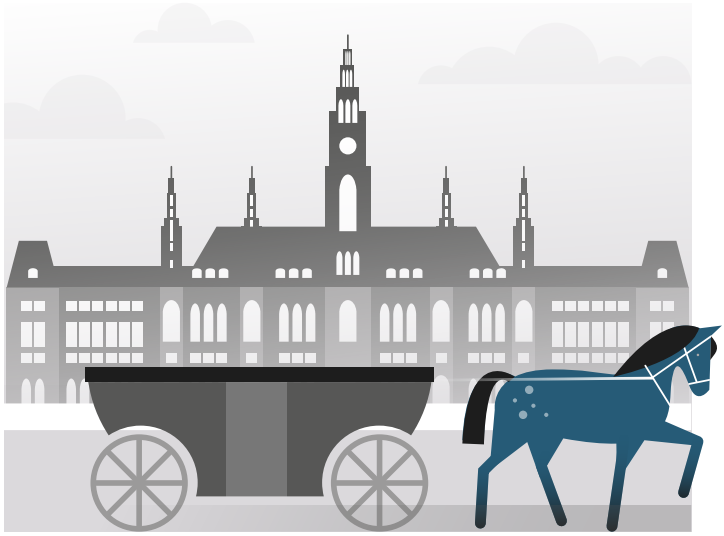
Worthy Winners at UEG Week 2018

EXCELLENCE across the field of gastroenterology was recognised at this year's UEG Week via presentation of three prestigious, individual awards. Best Research, Best Paper, and Overall Lifetime Achievement awards were the prizes on offer to many deserving nominees, leaving the deciding bodies spoilt for choice this year.

"I hope that this work can contribute to the pioneering research on building personalised models of coeliac disease, which can be utilised in many different ways."

Firstly, the 2018 UEG Research Prize was awarded to Prof Cisca Wijmenga, Lodewijk Sandkuijl Endowed Chair and Professor of Human Genetics, University Medical Centre Groningen, Groningen, Netherlands. As recognition for excellence in her outstanding work investigating a coeliac mucosal barrier-on-chip model in coeliac disease initiation, Prof Wijmenga was presented with €100,000. "I hope that this work can contribute to the pioneering research on building personalised models of coeliac disease, which can be utilised

in many different ways," she commented. Devoting much of her career to identifying novel genetic factors that underlie coeliac disease to better the lives of coeliac patients, as well as being the first to understand the power of genome-wide association studies using cases versus controls, Prof Wijmenga's interdisciplinary work makes her a worthy winner of the UEG Research Prize. Also appointed Knight in the Order of the Dutch Lion this year for exceptional service to the Dutch community, Prof Wijmenga is at the height of her career and her work will have a crucial impact on digestive health for years to come.



"I am honoured and humbled to receive such a prestigious award and extremely grateful to the Council for bestowing on me this unique Lifetime Achievement Award."

Recognising high-quality, significant research published in the UEG Journal during the past year, this year's UEG Journal Best Paper Award was presented to the first named author of the article entitled 'Correlation between adenoma detection rate in colonoscopy and faecal immunochemical testing-based colorectal cancer screening programs'. Lead author Joaquín Cubiella, Complexo Hospitalario Universitario de Ourense, Ourense, Spain proudly received the award for his team's post-hoc analysis of the COLONPEV trial, involving 5,722 patients to investigate adenoma detection rate in primary and work-up colonoscopy. Known for being one of the most significant colorectal cancer screening projects, Dr Cubiella commented on the importance of the COLONPREV trial: "This study will complete the follow-up in the coming years and will provide relevant information on the effect of the two most accepted screening strategies: colonoscopy and faecal immunochemical test."

The third and most prestigious standalone award presented at the annual UEG Week event is the UEG Lifetime Achievement Award, which acknowledges remarkable individuals who have contributed greatly to the UEG community, as well as to the entire field of gastroenterology and hepatology.

Remarkable leader and UEG President 2012-2013, Prof Colm O'Morain was announced as this year's Lifetime Achievement Award winner for his outstanding and essential contributions to research and public affairs. Spending a large proportion of his career at the Faculty of Health Sciences at Trinity College, Dublin, Ireland, Prof O'Morain has played an integral part of *Helicobacter pylori* investigations across the world, being the first to establish that *H. pylori* eradication can cure peptic ulcers, for example. He has also made large contributions to inflammatory bowel disease studies throughout Europe. "I am honoured and humbled to receive such a prestigious award and extremely grateful to the Council for bestowing on me this unique Lifetime Achievement Award. It is the pinnacle of my career and I hugely appreciate the nomination by the European Helicobacter pylori Study Group (EHSMG) and the Irish Society of Gastroenterology who put me forward as their candidate," said Prof O'Morain upon receiving his award. Advocacy work has also played a large part of Prof O'Morain's life, initiating colorectal cancer screening on both a national and pan-European level and calling for increased funding for health research as part of his active role in the European Parliament. Clearly an extremely deserving winner of this highly respected award, Prof O'Morain was lastly recognised for his major improvements to patient care across the field of gastroenterology, with many achievements that will inspire and encourage future generations of clinicians and researchers. Looking to the future, he concluded: "There have been great strides in medical care during my lifetime, but I expect more from the next generation and hope that UEG continues to flourish and excel."

"There have been great strides in medical care during my lifetime, but I expect more from the next generation and hope that UEG continues to flourish and excel."

Work–Life Balance: Tips from the Experts

Have you been asking yourself whether it is possible to be incredibly successful in both your family life and as a gastroenterologist? Well, part of UEG Week is the Young GI Network, which is intended to support congress attendees aged <40 years and give them the opportunity to network with both their peers and seniors, as well as receiving career tips and guidance. This year's UEG Week saw several Facebook live discussions as part of the Young GI Network's activities. One such discussion was on the topic of how to balance work and personal life. The experts discussing the topic were Prof Carolina Ciacci, University of Salerno, Salerno, Italy, and Prof Péter Hegyi, University of Szeged, Szeged, Hungary.

The first question the experts were asked was whether a choice had to be made and whether something had to be sacrificed. Prof Hegyi explained that this was a matter of prioritisation and focussing on the task at hand, which was a theme returned to often throughout the course of the discussion. He elaborated that when you were at work, you should be focussed on work, when you were at home with your family, you should be focussed on being a parent, and when you were on the sports field, you should be focussed on that. Prof Ciacci largely concurred with this statement, explaining that multitasking was a confusing message as "you cannot be at home and at work at the same time." She did however acknowledge that forgetting about work was the part she found the hardest.

Ways to ensure your time was as productive as possible were also suggested by the experts. Both extolled the virtues of outsourcing or delegating work that you did not necessarily need to do yourself. Prof Hegyi described saying 'no' to such tasks as being the biggest challenge of the twenty-first century. When combined with prioritising, delegating represents a powerful tool.

It may, however, be difficult for younger gastroenterologists to delegate as effectively if they have fewer people they are able to delegate to or perhaps lack the financial resources to outsource household tasks. Therefore, having a clear plan, as proposed by Prof Hegyi, is potentially a more useful tip. He declared that it was vital to have specific aims over a period of time, because otherwise you can be very busy but achieve nothing of value. Prof Hegyi also suggested that as part of this plan it was important to allot yourself some time in the day for other activities and that you should be strict with yourself about sticking to this. He mused on the importance of undertaking extracurricular activities, pointing out that, in his experience, most successful people took part in something else other than work. The need for a measure of flexibility in even the strictest of plans was highlighted by Prof Ciacci, who noted that if, for instance, your child has a problem at school and they call you, then all your plans must change immediately.

With many of the tips put forward by the experts somewhat dependent on personal circumstances, perhaps the most universally applicable suggestion was to ensure you are fully focussed on the situation in which you are currently in. This should ensure you are making the most of the time available to you. After all, as Prof Hegyi explained, sometimes you might technically be spending hours with your family, but if you are not focussed on them, you are not really present with them. If your priorities mean you must spend less time in a place, then having a 100% focus will maximise that time.

With many of the tips put forward by the experts somewhat dependent on personal circumstances, perhaps the most universally applicable suggestion was to ensure you are fully focussed on the situation in which you are currently in.

Buyer's Guide

- 3-D MATRIX
- 3D SYSTEMS SIMBIONIX
- ABBVIE
- ALFASIGMA SPA
- ALTON (SHANGHAI) MEDICAL INSTRUMENTS CO., LTD.
- AMG INTERNATIONAL GMBH
- AMGEN EUROPE GMBH
- ANKON MEDICAL TECHNOLOGIES
- ANREI MEDICAL (HANGZHOU) CO., LTD.
- APOLLO ENDOSURGERY
- ARC MEDICAL DESIGN
- BCM CO., LTD.
- BEIJING HUACO HEALTHCARE TECHNOLOGIES CO., LTD.
- BIOCODEX
- BIOGAIA
- BIOGEN INTL. GMBH
- BOSTON SCIENTIFIC INTERNATIONAL
- BÜHLMANN LABORATORIES AG
- CALPRO AS
- CANTEL
- CAPSOVISION, INC.
- CASEN RECORDATI SL
- CBC GROUP
- CELGENE CORPORATION
- CELLTRION HEALTHCARE
- CHANGZHOU DAHUA GROUP/CITEC
- CHANGZHOU JIUHONG INSTRUMENT CO., LTD.
- CHOYANG MEDICAL INDUSTRY LTD.
- COOK MEDICAL
- CREO MEDICAL LTD.
- DIVERSATEK HEALTHCARE
- DR. FALK PHARMA GMBH
- ELI LILLY AND COMPANY
- ELLA-CS, S.R.O.
- EMED SP. Z O. O. SP. K.
- ENDALIS
- ENDOAID LTD.
- ENDOCLOT PLUS, INC.
- ENDOSS
- ENDOTICS
- ERBE ELEKTROMEDIZIN GMBH
- EUROSPITAL
- EXALENZ
- FINEMEDIX CO., LTD.
- FISCHER ANALYSEN INSTRUMENTE GMBH
- FUJIFILM EUROPE GMBH
- GE HEALTHCARE
- GENETIC ANALYSIS AS
- GILEAD SCIENCES
- HANGZHOU AGS MEDTECH CO., LTD.
- HITACHI MEDICAL SYSTEMS/PENTAX EUROPE GMBH
- IMMUNDIAGNOSTIK AG
- INFAI GMBH
- INSITUMED GMBH
- INTROMEDIC CO., LTD.
- INVENDO MEDICAL GMBH
- JANSSEN
- JIANGSU ATE MEDICAL TECHNOLOGY CO., LTD.
- JIANGSU KANGJIN MEDICAL INSTRUMENT CO., LTD.
- JINSHAN SCIENCE & TECHNOLOGY
- KARL STORZ SE & CO. KG
- LABORIE
- LEO MEDICAL CO., LTD.
- LEUFEN MEDICAL GMBH
- LIFE PARTNERS EUROPE
- LUMENDI
- M.I. TECH CO., LTD.
- MAUNA KEA TECHNOLOGIES

- MEDI-GLOBE GMBH/ ENDO-FLEX GMBH
- MEDITALIA SAS
- MEDNOVA MEDICAL
- MEDTRONIC
- MEDWORK GMBH
- MICRO-TECH EUROPE GMBH
- MIRAI MEDICAL
- MSD (MERCK & COMPANY, INC.)
- MTW-ENDOSKOPIE
- MYLAN GMBH
- NET NEW ELECTRONIC TECHNOLOGY GMBH
- NEXTBIOMEDICAL CO., LTD.
- NIKKISO
- NISO BIOMED
- NORGINE
- NOVENTURE
- OLYMPUS EUROPE SE & CO. KG
- OVESCO ENDOSCOPY AG
- PENTAX EUROPE GMBH
- PETER PFLUGBEIL GMBH
- PFIZER
- PROBIOTICS INTERNATIONAL LTD.
- R-BIOPHARM AG
- RECKITT BENCKISER
- RICHEN MEDICAL SCIENCE
- ROBARTS CLINICAL TRIALS
- ROCHE
- ROGASKA DONAT MG
- S&G BIOTECH INC.
- SANDOZ INTERNATIONAL GMBH
- SHANGHAI ANQING MEDICAL INSTRUMENT CO., LTD.
- SHANGXIAN MINIMAL INVASIVE INC.
- SHENZHEN ZHONGHE HEADWAY BIO-SCI & TECH CO., LTD.
- SHIONOGI LTD.
- SHIRE
- SMART MEDICAL SYSTEMS LTD.
- SOFAR SPA
- SOLUSCOPE
- SONOSCAPE MEDICAL CORP.
- STANDARD SCI-TECH INC.
- STEELCO SPA
- SUMITOMO BAKELITE CO., LTD.
- SURGICAL SCIENCE
- TAEWOONG MEDICAL
- TAKEDA PHARMACEUTICALS INTERNATIONAL AG
- THE STANDARD CO., LTD.
- US ENDOSCOPY
- W. L. GORE & ASSOCIATES
- WASSENBURG MEDICAL BV
- WEGO GROUP
- WILSON INSTRUMENTS (SHA) CO., LTD.
- ZEON MEDICAL INC.

VIEW CONGRESS REVIEW ←

Interviews

Delve into the minds of our esteemed *EMJ Gastroenterology* Editorial Board members as we bring you sneak peaks and snippets from their lives thus far...

Featuring: Prof Oliver Grundmann, Dr Christoph Gubler, and Dr Devika Kapuria

Prof Oliver Grundmann

University of Florida, USA

How did you begin your medical career and what drew you to specialise in pharmacology?

A passion for natural sciences in middle and high school and spending a social year working in a hospital in an internal medicine department shaped my initial interest in the healthcare sector. Choosing the profession of pharmacology was ultimately a combination of my deep interest in pharmaceuticals and a desire to help people in their everyday life. At that point, I saw myself as a pharmacist working in a pharmacy and primarily assisting and consulting patients with advice on medication therapy management.

During my pharmacy studies at the Westfälische-Wilhelms-Universität, Münster, Germany, my interest in pharmacology and pharmacognosy became the primary focus of my studies. Although we have made so much progress in our understanding of drug design and development, the wave-like pattern of high-throughput screening of drug databases and natural products as lead structures has at times left us struggling to invent novel therapies, identify better targets, or advance patient well-being.

"Choosing the profession of pharmacy was ultimately a combination of my deep interest in pharmaceuticals and a desire to help people..."

Pharmacology is, in my opinion, not a singular discipline but rather combines multiple developments from all areas of natural sciences that can be applied to complex physiological and pathophysiological processes in the human body. With its origin being defined as the actions of a substance on a living being, pharmacology connects nearly all branches of medicine and healthcare with the patient at the very centre.

Some of your medical training took place in Münster. How did your European training differ from that in the USA?

The educational system in Europe differs from the USA in emphasising a natural science foundation more so than a clinical focus. In addition, students are directly entering their field of study after graduating high school, rather than taking general education classes as is customary in the USA. There is now a more clinical focus placed on pharmacy education in Germany and other European countries that mirrors that of the USA pharmacy education while the scientific foundation remains.

In retrospect, this has prepared me for a breadth of knowledge in areas that are not taught in the USA but are traditionally associated with the pharmacy profession, especially pharmacognosy and knowledge of herbal medicine and supplements, which has been removed from the curriculum altogether due to a lack of evidence-based medicine for a wide range of such supplements. The emergence of evidence-based approaches to evaluating treatment options has certainly influenced the landscape of therapy management.

For clinical pharmacists, however, the system in the USA certainly provides the benefit of being patient-centred and geared to prepare pharmacists for counselling, both in hospital and other healthcare settings. In addition, the collaborative nature of healthcare professionals is fostering a more inclusive environment that is now being cautiously adopted by some European universities as well. Overall, each system has its pros and cons based on tradition and social needs. A better approach for each system may be to separate the role pharmacists play as healthcare providers and their role in industrial drug development.

Is there a significant difference in guidelines between Europe and the USA when it comes to gastroenterology from a pharmaceutical perspective?

The complexity of guidelines, position papers, clinical practice recommendations, and consensus papers may at times be overwhelming to the clinical practitioner, both in the European Union (EU) and the USA. A comparison between the number of guidelines available on the website of United European Gastroenterology (UEG) and of the American College of Gastroenterology (ACG) makes clear that both the breadth and depth of guidelines available in the EU (251 available guidelines, consensus papers, and clinical practice recommendations) at this point addresses more topics than are being covered in the USA (42 guidelines published or in development). Many of the EU guidelines go into further detail on diagnostic and treatment criteria and often offer consensus developments among multiple institutions across different countries. This approach is similar to USA guidelines that were developed in collaboration with other professional organisations. Treatment approaches in general evolve around outcome measures of effectiveness for both the EU and the USA and rank such measures according to available scientific evidence. In both systems, the occasional economic impact of specific treatments may be mentioned, especially if their effectiveness is questionable or not considered first-line.

Some of your research has involved the impact of complementary and alternative medicine on irritable bowel syndrome and gastrointestinal (GI) cancers. What current and future applications do you see in the field of gastroenterology, especially in clinical practice, for complementary and alternative medicine?

The use of complementary and alternative medicine by patients is steady or rising for various reasons, which have been investigated by myself and colleagues. While herbal medicine has been a part of medical prescribing practices in most European countries, the USA has not embraced this traditional use of herbal extracts or other practices, such as aromatherapy, acupuncture, or chiropracty. In recent years, there has been a move towards integrative medicine among practitioners that seeks to establish best practices for certain complementary medical approaches with pharmacotherapy. Studies have indicated that integrative medicine provides patients with benefits in quality of life and subjective measures while maintaining

standards of care. Furthermore, it allows clinical practitioners to closely monitor and work more directly with patients on a treatment plan. The concern of undisclosed use of complementary medicines, especially herbal and dietary supplements, are often supplement–drug interactions that can either lead to reduced effectiveness, treatment failure, or even severe adverse effects.

Given the broad symptomatology of gastroenterological disorders, an individualised treatment approach following differential diagnosis can often provide both patient and provider with a better resolution when using an integrative approach. Licensed complementary practitioners can address subjective outcome measures of visceral pain, quality of life, appetite, taste, and others. In addition, there are now evidence-based clinical studies that provide indications of benefits of integrative medicine for several disorders such as functional bowel disorders, small intestinal bacterial overgrowth, irritable bowel syndrome, and even GI cancers.

In your opinion, what has been the most significant breakthrough in GI pharmacology in the past 5 years?

Admittedly, I am a bit biased since this topic has been on my radar for some time, but I believe that a significant discovery and breakthrough in recent years has been the GI microbiome and its unique composition. Over previous years, various research groups have mapped out the diversity of the microbiome and its vast contributions and interactions with human health and disease. The gut–brain axis was well known before these revelations, but, with the discovery of the more diverse microbiome, the intricate fine-tuning of the gut–brain axis now has taken on another meaning. Furthermore, inflammatory processes are now studied within not only the intestinal wall or the local immune system but can also be extended to the composition of the bacterial microflora that can contribute to the specific immune reaction. This can help to explain why certain groups are more vulnerable to developing specific GI disorders.

Gastroenterologists must reach and explore the full scope of how intricately the GI microbiome is linked to human health and disease. Its involvement in obesity, diabetes, and cardiovascular disorders has already been established and more such links are likely to emerge in years to come. I am truly excited about this development.

"...I believe that a significant discovery and breakthrough in recent years has been the GI microbiome and its unique composition."

Many of the pharmacotherapies used to treat GI disorders are well established and have been in clinical use for a long time. What exciting new therapies do you think will emerge within the next 5–10 years that will change treatment outcomes?

Personalised pharmacotherapy is already entering a stage in treatment that is more commonly applied depending on predispositions and specific genetic markers. I believe that precision medicine and personalised pharmacotherapy will advance treatment outcomes and reduce adverse effects in general, not only in gastroenterology.

Another area that has been researched heavily is autoimmune disorders with identified gene defects (e.g., Crohn's disease, haemochromatosis, autoimmune hepatitis, and polycystic liver disease) that can be treated with gene therapy. Although still in its infancy, the first gene therapy was approved by the U.S. Food and Drug Administration (FDA) in 2017 for an inherited disorder. The concept has long been known and many targets have been identified.

What are the most valuable contributions that a pharmacist and healthcare provider such as yourself can make to GI patient care to improve outcomes?

Patient care is a collaborative approach for a healthcare provider team. In my role as an academician, the training of pharmacists to counsel patients and other healthcare providers on pharmacotherapy, providing an open dialogue for communication, and conducting research that will allow pharmacists and other

healthcare providers to optimise treatment outcomes are central. In this regard, access to medications and other services, especially counselling on available integrative medicine options, is linked to my ongoing research efforts. As a result of my dual education in Europe and the USA and the high degree of utilisation, yet often a lack of education in complementary medicine, I work with pharmacy and other healthcare students at my institutions to provide them with knowledge on integrative medicine to better counsel their patients. The ongoing research efforts are often directly applicable to improving GI patient outcomes as they focus on optimising quality of life in GI cancer patients and evaluating integrative medicine use.

"Patient care is a collaborative approach for a healthcare provider team."

You have an interest in teaching and developing online classes, as well as medical curricula more generally. What are the most important considerations when developing an effective training course?

Over the past 10 years working in graduate, professional, and online education there have been many challenges and 'trials and tribulations' that one can learn from. Similar to a patient-centred approach in clinical practice, teaching needs to be learner-centred. Together with other faculties and as the director of two graduate programmes, we have developed curricula that are geared towards working with professionals, such as nurses, physicians, and pharmacists. We are providing content in a flexible and, pardon the pun, digestible format that allows them to study in their own time. With learners from 45 different countries, the format had to be asynchronous while at the same time providing a sense of community with technological tools to connect learners. The knowledge community in our courses is often an organic, natural process among learners where we come together as a group and exchange insights from our clinical practice. As a result, every semester is a new dynamic and a new experience for both myself and learners alike. In graduate and professional education, aside from individual assessment and meeting standards of achievement, the goal is to provide learners with practical and applicable knowledge that they can take with them into their practice: teaching with a purpose, if you will. This approach has worked very well in my courses. That being said, there is always room for improvement.

What is your favourite topic to teach and why?

Interestingly enough, my favourite topic is unrelated to gastroenterology: it is drugs of abuse. Pharmacology has always been my main attraction since my pharmacy studies and during my graduate studies I also undertook a Master's programme in forensic toxicology, which led me to the fascinating world of drugs of abuse. I have been teaching courses related to this topic on the undergraduate, professional, and graduate level ever since I started teaching and learners appear to be as fascinated by it as I am. In an undergraduate Honours reading class we used 'Beautiful Boy' by David Sheff to discuss the complexity of drug dependency and substance abuse. In a Doctor of Pharmacy elective course, we connect the pharmacology of common pharmaceutical drugs to those of drugs of abuse. Learners are always fascinated by some of the facts and the lively discussions that we have in class. The graduate course is training professionals in crime laboratories and healthcare providers working in emergency departments to be better informed about drugs of abuse, their symptoms, pharmacokinetics, and treatment options.

What are three key qualities one requires to be an effective pharmacist?

Patience, empathy, and, as for all healthcare professionals, incredible memorisation and recall skills.

"The knowledge community in our courses is often an organic, natural process among learners where we come together as a group and exchange insights from our clinical practice."

Dr Christoph Gubler

University Hospital Zurich, Switzerland

To begin, could you talk us through how you became interested in gastroenterology? Was there a specific person or event that inspired you to pursue a gastroenterology-focussed career?

I was convinced to become a visceral surgeon and started my clinical work in surgery. At that time the hierarchic system did not allow me to move further and I changed into internal medicine. Missing manual challenges, I was checking out particular specialities. When I saw my first endoscopic retrograde cholangiography (ERC) as a resident, I realised the potential of endoscopy and interventional endoscopy even more. It is the perfect mix of medicine and surgery.

Gastroenterology is an ever-evolving discipline. What do you believe to be the most pertinent discovery in the field over the last 10 years?

Two issues have been of utmost importance to evolve our discipline. The acknowledgment of the colonic microbiome for a wide variety of diseases not restricted to gastroenterology. Here we may expect some therapeutic interventions in the future. For sure in endoscopy the fast-developing technical option to see more, resect more, and advance into body cavities so far hidden from our eyes. Examples of the aforementioned innovations are zoom endoscopy with virtual staining, endoscopy submucosal dissection, and pancreaticoscopy.

Last year, you published a paper on severe infectious complications after endoscopic ultrasound-guided fine needle aspiration. Could you summarise the results of this case series and the conclusions that can be drawn for future procedures?

We did few endoscopic ultrasound-guided cyst injections in the peri-oesophageal region and the mediastinum over the last 15 years. Although we followed the guidelines by application of peri-interventional antibiotics, four out of five patients developed severe complications with long hospital stay and the need of surgery. Therefore, we strongly recommend omitting fine needle aspiration in cases of suspected duplication cysts within the oesophagus. A watch and wait strategy or straight forward resection are better options.

With the ever-increasing obesity epidemic, bariatric surgery is becoming increasingly common, and with that, undoubtedly, come associated complications. What are the most common bariatric surgery complications and how they can be avoided?

Leakages in the early and late period postoperative are definitely the most feared and even most common events. Secondly, bleeding from the anastomoses occur and, in the long run, dumping syndrome in bypass patients might be an issue. Up until now, no proven intervention or technical adaption is known to prevent such complications. With the number of these operations increasing, we are certain to be faced with such clinical situations in our daily routine. Early detection has an impact and may shorten the course of this particular syndrome.

A recently published paper using endoluminal vacuum therapy for wound healing after oesophagogastric surgery concluded that it is a safe and effective treatment for upper gastrointestinal leaks. What are your opinions on the use of this new therapy and its potential implications?

We have used endoluminal vacuum therapy for years routinely at our centre for any leakages in the upper and lower gastrointestinal tract. We sometimes combine it with over-stenting (so called SOS [Stent over Sponge]) to force

negative pressure in the cavities. Sponges have to be tailored in size and shape considering the intended placement in the lumen or cavity. I strongly recommend favouring the vacuum device over any closing device such as stents, clips, or stitches.

One of your interests is the use of ERC techniques in balloon dilatation. Could you explain what is most exciting about this technique?

Every interventional gastroenterologist is familiar with the large stone situation, so called complex bile duct stones. Every stone >1 cm in diameter may pose surprising obstacles within seconds. Some are easy to fragment and extract, but some ERC may develop into a very uncomfortable situation. Different lithotripsy techniques and devices are available, but the dilemma remains: a small ostium, called the papilla, hinders the removal of a large stone. Large amounts of cutting at the papilla bears a substantial risk of bleeding and perforation. A suitable solution is the combination of a restricted cut with a smooth dilatation; data from the Far East have already shown better stone clearance with higher safety profile.

Which gastroenterological disease or condition do you think warrants more research?

In my opinion, one condition that is completely misunderstood is the first hit of acute pancreatitis and its prevention. Why do some patients develop severe pancreatitis after a simple and fast ERC without any part of the pancreatic opening being touched, and others do not? To focus on the prophylaxis of the post ERC pancreatitis we need first to understand the mechanism of the cascade and its trigger.

Is there any research currently ongoing that you are particularly looking forward to seeing the results of?

I am really excited about long-term data of cohorts to come in the field of surveillance of branch duct intraductal papillary mucinous neoplasm and of different types of endoscopically resected gastrointestinal tumours. We really need robust long-term data, over more than 5 years, to adapt our surveillance policy or referral behaviour for surgery.

What do you consider to be the biggest achievement in your medical career so far?

It is the sum of all my clinical years of teaching those who are now young gastrointestinal doctors how to approach patients and to use all of our available instruments wisely. I am proud of every former resident who is brought to a leading position.

Finally, if you could give one piece of advice to a budding gastroenterology student, what would it be?

Stay focussed on medicine itself and ignore economical considerations, and, importantly, always try to understand the problem before running into activity.

Dr Devika Kapuria

University of New Mexico, USA

What led you to begin a career in gastroenterology?

Gastroenterology was the first clinical rotation I had as a medical student and the close link between the intellectual and procedural aspects of the field fascinated me. As I progressed through my medical career, the diverse avenues for research and clinical practice, as well as the exponential growth in scientific breakthroughs

in the field and the scope of specialisation, made gastroenterology a very attractive career choice for me.

The gut–liver axis is of increasing interest to researchers. What breakthroughs do you hope to see from the examination of this relationship in the next decade?

The cross-talk in the gut–liver axis has progressed from observational studies to interventional research in murine models of human disease. Animal models with humanised microbiomes are already being used to learn more about the role of the microbiome in diseases such as hepatocellular carcinoma. I anticipate the development of refined microbiome models specific for different human diseases. Faecal microbiota transplantation will play a more important therapeutic role in various diseases. Large scale clinical trials using well-defined microbiome-based therapeutic and prognostic modalities for the treatment of liver diseases, particularly for nonalcoholic steatohepatitis, are expected in the not-so-very distant future.

You note in a recent paper that 'the liver is the site where the systemic immune system meets translocated bacterial products and intestinally derived inflammatory markers'. To what extent does the gut microbiome play a role in liver disease related to immunodeficiency?

The gut microbiome is important for the maturation of the immune system; it has been demonstrated that germ-free mice fail to develop lymphoid follicles and are deficient in secretory IgA, which can be reversed by colonisation of these mice with commensal bacteria. It has also been shown in common variable immune deficiency that microbiome changes can influence B cell development and T cell pathology. In a seminal study by Jørgensen et al.,[1] the gut microbiota in patients with common variable immune deficiency was found to be significantly different compared to healthy controls, and patients exhibiting the most complications were found to have profound dysbiosis and elevated markers of immune activation. Additionally, low alpha diversity in these patients was associated with higher levels of lipopolysaccharides and serum and soluble CD25, both markers of inflammation. Further studies looking at the gut microbiome in other primary immunodeficiencies and the effects of altering the gut microbiota should be considered.

"Faecal microbiota transplantation will play a more important therapeutic role in various diseases."

Research is also beginning to shed light on the interplay of the gut and liver with other organ systems, such as the pulmonary and cardiovascular systems. Looking to the future, do you believe gastroenterologists will be required to take part in interdisciplinary discussions more regularly than at present to deliver care?

The relationship of the liver with lung disease such as hepatopulmonary syndrome, as well as portopulmonary syndrome, has been well recognised, as well as the increased prevalence of coronary artery disease in advanced liver disease. Additionally, there is increasing evidence of even milder, less advanced stages of liver disease being associated with systemic complications. This makes it necessary for the gastroenterologist to be aware and participate in discussions with not only the patient but also their primary care providers and other specialists regarding the risk of associated complications due to the patient's underlying liver disease.

You recently published a paper on the association of hepatic steatosis with subclinical atherosclerosis. Could you briefly describe your findings and what implications these have for the future research into nonalcoholic fatty liver disease (NAFLD)?

We wanted to look at real-world markers of subclinical coronary artery disease and see whether the presence of NAFLD predisposed people to subclinical atherosclerosis. We combined data from 12 studies that looked at the prevalence of subclinical atherosclerosis

using coronary artery calcification as a quantification method and found that having NAFLD increased the risk of having subclinical coronary artery disease by as much as 1.6-times. This further intensifies the need for new innovations from researchers in the field of NAFLD, especially given the increasing burden of liver disease and the worrisome implications it has in several aspects of human disease.

The incidence of NAFLD is increasing across the globe. What implications does this have for the medical profession and what steps are being taken to improve this situation?

The alarming rate of increase of NAFLD across the globe presents some worrying projections for human health. Markov models based on published literature show that the number of NAFLD cases will increase by a whopping 21% to approximately 100 million people by 2030.[2] Also, liver-related deaths are expected to increase by 178% by 2030 in the USA alone.[2] These numbers are troubling for gastroenterologists and the entire medical community. Fortunately, this problem is now being recognised and NAFLD research is getting increasing allocations for the development of new drugs to mitigate this problem. However, lifestyle changes remain the only proven method for management of NAFLD, and more needs to be done to create integrated centres for NAFLD management with a multidisciplinary approach to helping affected individuals.

"Social media has brought about a huge change in how we can access new medical information."

One of your other interests is the use of biosimilars to treat inflammatory bowel disease (IBD). How have biosimilars impacted the treatment of this condition?

The shift to biosimilars may be challenging for both physicians and patients. While safety concerns related to biosimilars have been alleviated following post-marketing studies from Europe, there still remains a significant lack of awareness about biosimilars among healthcare providers, especially about prescribing and administering them. Patient acceptance remains an important aspect as well, with several patients loyal to the reference brand who may not have the same level of confidence in the biosimilar. Also, patients may believe that biosimilars are, in some way, inferior to the reference product.

"It is an exciting time to be in gastroenterology: hepatitis C has just been conquered and artificial intelligence has entered the realm of medicine."

With only single entrants per category in the USA, biosimilars are priced at 15–20% lower than their brand name rivals, which, though cheaper, still amounts to hundreds of thousands of dollars. By the end of 2016, the estimated global sales from biosimilars amounted to $2.6 billion, and nearly $4.0 billion is projected by 2019.[3] There are both human and economic factors to be considered in this rapidly growing field; increased awareness among prescribers and patients about the safety and efficacy of biosimilars as well as improved regulatory aspects are essential for the widespread adaptation of biosimilars.

Are there any gastroenterological conditions that you think warrant greater research than is currently underway?

Gastrointestinal motility is still a niche field in gastroenterology. I think that more research in diagnosing and managing patients with gut motility disorders is needed.

You are quite an active Twitter user; to what extent has the use of social media changed the field of gastroenterology?

Social media has brought about a huge change in how we can access new medical information. Every major journal now has multiple social media accounts. Instead of waiting for a new edition of a journal to be published, I now subscribe to the Twitter feed of the journal I am interested in and get real-time updates on what is fresh-off-the-press. Not only this, lots of people now participate in what I can only

describe as 'mini impromptu journal clubs', wherein a new study and/or trial is discussed by a wide variety of healthcare professionals from all over the world.

Finally, what advice would you give to young gastroenterologists just beginning to enter the field?

It is an exciting time to be in gastroenterology: hepatitis C has just been conquered and artificial intelligence has entered the realm of medicine. Very soon, artificial intelligence may be involved in colonoscopies and capsule endoscopies and perform a better job at recognising polyp patterns than us. It is therefore, important to recognise that our chief role remains to be a physician and to develop diagnostic and clinical skills that will lead to a successful and fulfilling career.

References

1. Jørgensen SF et al. Altered gut microbiota profile in common variable immunodeficiency associates with levels of lipopolysaccharide and markers of systemic immune activation. Mucosal Immunol. 2016;9(6):1455-65.
2. Estes C et al. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology. 2018;67(1):123-33.
3. Winegarden W. Impediments to a Stronger Biosimilars Market: An Infliximab Case Study. 2018. Available at: https://www.pacificresearch.org/wp-content/uploads/2018/06/PolicyObstaclesFweb.pdf. Last accessed: 28 August 2018.

VIEW MORE INTERVIEWS ONLINE ←

A Worldwide Perspective on Diagnosis and Management of Diverticular Disease: Understanding Similarities and Differences

This symposium took place on 22nd October 2018, as part of the 26th United European Gastroenterology (UEG) Week in Vienna, Austria

Chairpeople: Fermín Mearin[1]

Speakers: Fermín Mearin,[1] Giovanni Barbara,[2] Kok Ann Gwee,[3] Neil Stollmann[4]

1. Institute of Functional and Motor Disorders, Centro Médico Teknon, Barcelona, Spain
2. Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
3. Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
4. Division of Gastroenterology, Alta Bates Summit Medical Center, Oakland, California, USA

Disclosure: Dr Mearin has served as a consultant, advisory board member, and speaker for Alfasigma and Allergan. Dr Barbara has served as a consultant, advisory board member, and speaker for Alfasigma, Allergan, Cadigroup, Danone, Yakult, Ironwood, Malesci, Nestlé, Noos, Shire, Sofar, and Synergy. Dr Gwee has served as a consultant, advisory board member, and/or speaker for Alfasigma (advisory board, consultancy, speaking honorarium), Biocodex (advisory board, speaking honorarium), EA Pharma (advisory board), Eisai (education grant), Lonch Pharmaceutical (advisory board, consultancy), LF Asia (education grant), Menarini Asia-Pacific (advisory board, speakers' bureau, consultancy), and Pfizer (advisory board, speaking honorarium). Dr Stollman has served as a speaker for Alfasigma.

Acknowledgements: Writing assistance was provided by Iain O'Neill, who was working as a freelance writer on behalf of IntraMed Communications Srl, Milan, Italy.

Support: The symposium presentation and publication of this article were funded by Alfasigma SpA, Bologna, Italy. The views and opinions expressed are those of the authors and not necessarily of Alfasigma SpA.

Citation: EMJ Gastroenterol. 2018;7[1]:40-48.

Meeting Summary

The epidemiology of diverticular disease (DD) is changing, with an increasing prevalence in younger patients from Europe and the USA, and changing disease patterns also seen in Asian populations. This epidemiological shift has substantial implications for disease management policy and healthcare costs. Most (75–80%) patients with diverticulosis never develop symptoms. Around 5% develop acute diverticulitis or other complications, while 10–15% develop symptomatic uncomplicated DD (SUDD) with symptoms resembling irritable bowel syndrome (IBS). However, most available guidelines highlight the importance of diverticulitis, with less emphasis on and often limited discussion about SUDD and its management. Recent data suggest an important relationship between gut microbiota and DD, including SUDD. In healthy individuals, the gut microbiota exists in harmony (eubiosis); in individuals with disease, quantitative and qualitative changes in microbial

diversity (dysbiosis) may adversely influence colonic metabolism and homeostasis. Addressing this imbalance and restoring a healthier microbiota via eubiotic or probiotic therapy may be of value. In SUDD, clinical benefit has been seen with the use of rifaximin, which acts by multiple mechanisms: direct antibiotic activity, a modulatory eubiotic effect with an increase in muco-protective *Lactobacillus* and *Bifidobacterium* organisms, and anti-inflammatory effects, among others. Clinical studies have demonstrated symptom improvement and reduction in complications in patients with SUDD, with a favourable safety and tolerability profile and no evidence of microbial resistance. Evidence for other agents in DD is less robust. Mesalamine is not effective at preventing recurrence of acute diverticulitis, although it may provide some symptom improvement. At present, there is insufficient evidence to recommend the use of probiotics in SUDD symptom management.

Introduction

Colonic diverticula are herniations of the colonic mucosa and submucosa through the colonic wall. Colonic diverticulosis is common with increasing age, and while most individuals with diverticulosis remain asymptomatic, 10–35% will develop symptoms of DD.[1] Of these patients, 85–90% will develop symptomatic SUDD and 10–15% will develop acute inflammatory and possibly sub-colitic changes, chiefly acute diverticulitis, with or without complications, which include abscesses, fistulae, and perforation (Figure 1).

SUDD is defined as persistent and recurrent abdominal symptoms attributed to diverticula in the absence of obvious inflammatory changes in the colonic mucosa. The cardinal symptom of SUDD is abdominal pain or fullness, often accompanied by bloating and bowel habit abnormalities. There is a wide overlap between SUDD and IBS, both in terms of symptoms and management. This overlap is well recognised, although patient profiles (generally SUDD patients are older) and clinical features, especially those related to abdominal pain severity, which is substantial in SUDD; location of the pain (more diffuse in IBS, but localised to the lower left quadrant in SUDD); and duration of pain (>24 hours in SUDD) may help distinguish between SUDD and IBS. Other parameters, such as faecal calprotectin levels (sometimes elevated in SUDD but rarely in IBS), are also helpful.[1,2] An additional consideration is that IBS-like symptoms may emerge after acute diverticulitis.[3]

A number of published guidelines or consensus statements on the diagnosis and treatment of DD are available from Europe[2,4-8] and the USA.[9,10] There are no specific guidelines from Asia, although discussion of DD in Asia is included in guidance from the World Gastroenterology Organisation (WGO).[11] Most guidelines focus principally on acute diverticulitis (treatment and primary and secondary prevention), and specific discussion on diverticulosis and SUDD is often lacking.[12] Notable exceptions are the most recent consensus statements from Italy and Poland.[2,7,8] SUDD is not discussed in the current USA guidelines because the currently available evidence was considered limited.[10]

Epidemiological Aspects of Diverticulosis and Diverticular Disease

Diverticulosis shows an age-dependent distribution, with a prevalence reaching 60% in individuals >80 years old.[13] However, epidemiological data suggest an increasing prevalence of diverticulosis and DD in younger patients.[14] In Italy, recent data indicate an increase in hospitalisation for acute diverticulitis from 2008–2015 (from 39 to 48 per 100,000 inhabitants) and while hospitalisation rates remained relatively stable in patients aged >70 years, a significant increase in hospitalisation rates due to acute diverticulitis in younger patients (including those aged 18–39 years) was observed.[15] Other Italian data also report increasing numbers of admission due to complicated disease in younger patients.[15,16] A corresponding increase in health-system costs has also been seen, and although much of the cost burden is due to complicated disease in older patients (especially those requiring surgical care), the hospitalisation costs associated with uncomplicated disease are also substantial.[16]

Recent colonoscopy surveillance data also show increasing prevalence of diverticulosis in some Asian countries (Singapore and Japan).[17,18]

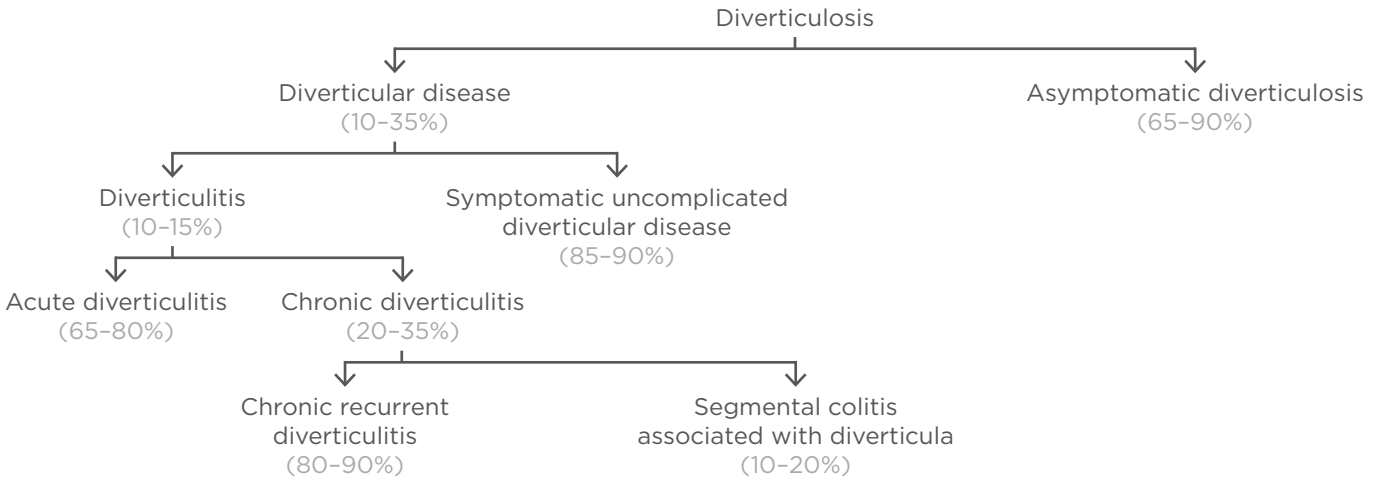


Figure 1: Taxonomy and relative frequency of diverticular disease.

Adapted from Scarpignato et al.[1] and Cuomo et al.[2]

There is substantial regional variation in the prevalence of diverticulosis across Asia, with higher rates in the Philippines, Singapore, Hong Kong, and Japan (ranging from 25–35%) and a far lower prevalence in India, China, and South Korea (1–3%).[17] Right-sided disease remains the predominant phenotype in Asia.[17] In Singapore, the prevalence of right-sided diverticulosis increased from 15% to 25% between 2006 and 2016; left-sided diverticulosis increased from 5% to 10%, and pan-colonic diverticula increased from 3% to 5%.[17] In contrast, in India, the prevalence of diverticulosis remained low and relatively stable between 2010–2015.[17] Singapore is a multi-ethnic society and an important observation is that increased prevalence of diverticulosis was seen across all three major ethnic groups: Chinese, Malay, and Indian.[17] Although speculative, it is possible that a rise in prevalence could follow the adoption of Western-style diets and the greater prevalence seen in Singapore, Hong Kong, the Philippines, and Japan may reflect this rather than any ethnic or genetic component. If this were the case, a concern is that, following any switch to such a diet, a higher prevalence may also arise in currently low-prevalence populations.

Data from Japan show that right-sided diverticulosis begins to occur before 39 years of age, with a prevalence of 4%, which increases at 40 years and 60 years of age to 10% and 16%, respectively. On the other hand, the prevalence of left-sided DD begins to increase from the age of 50 years, and progressively increases until beyond the age of 70 years.[18] In this study, alcohol consumption was a risk factor for right-sided disease, while smoking was a risk factor for both right and left-sided disease.[18] Another Japanese study found that left-sided and bilateral diverticulosis (but not right-sided disease) were associated with a higher risk of IBS.[19]

Pathophysiology Update

Studies have demonstrated increased intraluminal pressure and motility following provocative stimuli in patients with diverticula compared to healthy controls.[20] In Western populations, this involves the sigmoid region, while in Asian patients these features are seen also in the ascending colon in patients with right-sided diverticulosis.[20,21]

While age-related weakening of the colonic wall is an important feature of diverticulosis, this involves only the descending colon.[22] Minimal changes in colonic wall strength have been observed in the ascending colon in Western and Asian patients. While this may explain, in part, the left-sided predominance of diverticulosis in Western populations, the absence of weakening in the affected site in Asian patients highlights the role of other factors in disease mechanisms, including stool form and viscosity in different

colonic segments, as well as genetic and dietary components.[22] Other colonic tissue changes may also play a role; for example, altered extracellular matrix and collagen rearrangement predispose to increased rigidity and elastosis in the colonic wall.[2,20]

Pain is an important feature in SUDD. In patients with diverticulosis, an increase in the numbers and density of nerve fibres within the colonic mucosa is seen at affected sites. This is particularly evident in patients with SUDD, in whom increased nerve sprouting can also be demonstrated in the affected region, a feature less evident in asymptomatic disease.[23] It is possible that this may underlie pain transmission in SUDD patients, although further studies are needed to support this hypothesis. Measurement of visceral sensitivity by rectal distention has found that patients with symptomatic disease have lower pain thresholds than asymptomatic patients, along with increased expression of neuropeptides (e.g., neurokinin-1) in the colonic mucosa in symptomatic patients.[24]

The Intestinal Microbiome

The role of the gut bacterial microbiota in health and potential changes contributing to DD is growing in importance. The putative role of microbiota in the pathogenesis of DD is also supported by evidence that most disease complications (e.g., inflammation, fistulae, and abscesses) are of bacterial origin. The relationship between gut microbiota and disease may be considered as that of eubiosis, when there is a healthy quantitative and qualitative balance between microbiota and host metabolism and immunology, or dysbiosis, when quantitative and qualitative changes to gut flora are associated with altered colonic metabolism and immune function. Colonic microbiota is inherently linked to diet, with different compositions in populations with a diet rich in red meat and fat compared with those receiving a high-fibre diet.[25] Dietary fibre is an important source of energy for the gut microbiota and gut microbiota metabolise complex carbohydrates into short-chain fatty acids, which influence both mucus and antimicrobial peptide production.

Differences exist in the colonic microbiome in healthy subjects compared to that seen in patients with DD. For example, recent studies have shown that, compared with healthy subjects, an overgrowth of *Aeromonas* species (e.g., *A. muciniphila)* and higher relative abundance of *Bifidobacterium* are found in patients with acute diverticulitis or SUDD.[26,27] Other studies have shown a higher diversity of *Proteobacteria* and higher levels of *Actinobacteria* in patients with acute diverticulitis compared to those with uncomplicated diverticulosis.[28,29] Another recent study examined colonic mucosal biopsies and also the faecal microbiome in patients with diverticulosis or SUDD.[30] Microbiome analysis showed that patients with diverticulosis had a microbiota enriched in *Bacterioides* and *Prevotella* (encompassing several groups of bacteria with proinflammatory properties), while patients with SUDD had depletion of a range of species (*Clostridium* cluster IV and IX, *Fusobacterium*, and *Lactobacillus* species) associated with anti-inflammatory pathways or production of muco-protective short-chain fatty acids. Biopsy comparisons found no differences in mucosal T cell or mast cell numbers, but a >70% increase in colonic macrophages was seen in patients with diverticulosis and SUDD (at affected and at distant sites).[30] This suggests a potential role for mucosal macrophages as a marker for DD.

It must be remembered that these findings do not indicate causality, and other studies have found no associations between microbiota composition changes and disease.[31] Most studies examining such associations are small, and dietary changes and treatment of DD may have contributed to changes in gut microbial ecology.

Controversies in Disease Management

Historically, antibiotics were considered a standard treatment for acute diverticulitis. However, data from two recent randomised clinical trials (RCT) have indicated little to no benefit from antibiotic administration in patients with acute uncomplicated diverticulitis.[32-35] In the AVOD study,[32] which compared observational management with or without antibiotics, there were no differences in reported

abdominal pain or tenderness during inpatient care, and both groups had similar durations of hospital stay. At 12-month follow-up, similar rates of complications, such as abscess, perforation (1–2%), and recurrent diverticulitis requiring readmission (16%), were reported.[32] In the DIABALO study,[33] which compared parenteral followed by oral antibiotics for 10 days versus observational care alone, no differences in time to recovery were seen for the two groups. However, the length of hospital stay was shorter in the observation group (2 versus 3 days; p=0.006).[33] Both groups had similar rates of complications, recurrent disease, and subsequent readmission at 6-month follow-up,[33] with similar rates of recurrent or complicated disease at 2 years.[34] While no significant differences in the need for sigmoid resection were found, a trend towards more elective surgery in the observation group was seen.[34] A recently published systematic review and meta-analysis has concluded that antibiotic use is not associated with reductions in rates of major complications, disease recurrence rates, or surgical resection, although antibiotic use may be associated with a significantly shorter duration of hospital stay.[35] These findings support the approach that antibiotics in patients with uncomplicated acute diverticulitis should not be used routinely, with selective use reserved for the treatment of those patients with complicated disease, severe infection/sepsis, or significant comorbidities. This is reflected in treatment recommendations in the current Dutch, Italian, German, and USA guidelines.[2,5,6,10]

The role of diet, including dietary supplements and foodstuffs to avoid, is frequently debated. Fibre assists in stool bulking and colonic motility and promotes the growth of beneficial colonic microbiota (e.g., *Bifidobacterium* and *Lactobacillus* species). For these reasons, a fibre-rich diet would seem to offer protective benefits against DD.[36] However, the evidence suggests different associations between fibre and diverticulosis and fibre and DD. For example, in the USA, the Diet and Health Studies III–V found that a high-fibre diet and increased frequency of bowel movements were associated with greater prevalence of diverticulosis.[37] In contrast, large prospective studies from the UK (EPIC-Oxford study)[38] and the USA (Health Professionals Follow-up Study)[39,40] have shown an inverse association between fibre intake and diverticular complications, in which high-fibre dietary intake is associated with reduced risk of hospitalisation for DD,[38] symptomatic DD,[39] and acute diverticulitis.[40] These somewhat contradictory findings suggest that the underlying mechanisms (and the influence of fibre) in the development of diverticulosis may be quite different to those involved in subsequent diverticulitis development; it would seem that fibre is of benefit in patients with DD and SUDD. The most recent guidelines from the USA suggest that a fibre-rich diet or fibre supplementation may be beneficial in patients with a history of acute diverticulitis.[10]

The evidence base for the role of fibre supplements is relatively limited and is principally from older studies, many of which have substantial methodological limitations, which leads to difficulty in drawing firm conclusions.[36] This was reflected in recent Italian guidelines, which concluded that fibre supplementation alone provides controversial results in terms of symptom relief for SUDD.[2]

While it has been proposed that certain foodstuffs (e.g., seeds, nuts, and popcorn) can predispose to DD, data from a large prospective cohort study show no increased risk of diverticulosis or DD; indeed, subjects with the greatest consumption of nuts or popcorn had significantly lower risk than those with lowest consumption.[41] This was reflected in the most recent USA guidelines, which recommended against advising patients with a history of acute diverticulitis to avoid nuts and popcorn.[10]

DD shows seasonal variation, and this could reflect sunlight exposure and vitamin D levels. A USA study found that patients with acute diverticulitis had significantly lower levels of vitamin D than those with diverticulosis, with the lowest levels seen in patients with complications or recurrent diverticulitis.[42] However, no direct causal relationship can be made and, at present, no recommendations regarding vitamin D supplements have been made.

Role of Rifaximin in the Management of Symptomatic Uncomplicated Diverticular Disease

Rifaximin is a poorly absorbed oral antibiotic characterised by non-systemic absorption and resultant high faecal concentration with broad antimicrobial activity (against Gram-positive and Gram-negative aerobic and anaerobic bacterial species).[43] Rifaximin acts via multiple mechanisms relevant to SUDD. In addition to overt antibiotic activity, rifaximin has a modulatory eubiotic effect on bacterial species, as seen in animal models and human clinical and metagenomic studies that have demonstrated an increase in *Lactobacillus* and *Bifidobacterium* after rifaximin treatment.[44,45] Anti-inflammatory effects are exerted via different pathways, including activity against proinflammatory gut microbiota.[43,46] An important mechanism is due to the role of rifaximin as a gut-specific ligand for the human nuclear pregnane-X receptor (PXR), expressed primarily in the gastrointestinal tract. PXR activation is considered critical for maintenance of intestinal integrity and in downregulation of inflammatory responses triggered by the gut microbes and NFκB-mediated proinflammatory cytokine pathways. Rifaximin-PXR binding can contribute to this.[46]

The effects of rifaximin in SUDD have been investigated in prospective RCT (three open trials and one double-blinded study involving a total of 1,660 patients),[47-50] and in a subsequent meta-analysis study.[51] In most studies, rifaximin was given with fibre supplementation (principally glucomannan, a highly soluble fibre), with the comparator group receiving glucomannan monotherapy; rifaximin was given as 400 mg twice a day for 7 days every month for 12 months (Table 1). Across these studies, symptom improvement (i.e., the number of patients free of symptoms for the previous 6 months) ranged from 56.5–89.7% in patients receiving rifaximin plus fibre (27–34% higher than that seen in the comparator groups receiving fibre only). In a meta-analysis, Bianchi et al.[51] pooled data from all four studies; at 1-year follow-up, 64% of patients treated with rifaximin plus fibre supplements were symptom-free versus 34.9% of patients receiving fibre alone. The pooled rate difference for complete symptom relief was 29.0% (95% confidence interval: 24.5–33.6; p<0.0001). This translates as a number needed to treat of 3.[51] In these studies, 2.8% of individuals in the comparator group developed acute diverticulitis compared with 1.0% of those receiving rifaximin, with a pooled rate difference of -1.9% (95% confidence interval: -3.4–[-]0.57%) in favour of rifaximin (p=0.006) and a number needed to treat of 50.[51]

Rifaximin was safe and well-tolerated in these studies, with no significant differences in adverse events observed in the different treatment arms.[51] A broader safety analysis of rifaximin in double-blinded, placebo-controlled trials in patients with DD or IBS found the safety and tolerability were comparable to placebo.[52]

Table 1: Prospective randomised trials of rifaximin in symptomatic uncomplicated diverticular disease.

Study	Patients	Study design	Treatment	Comparator	Duration	Symptom improvement	Net gain
Papi et al.,[47] 1992	217	Open	Rifaximin* plus glucomannan	Glucomannan	12 months	58% vs. 24%	34%
Papi et al.,[48] 1995	168	RCT	Rifaximin* plus glucomannan	Glucomannan plus placebo	12 months	69% vs. 40%	29%
Latella et al.,[49] 2003	968	Open	Rifaximin* plus glucomannan	Glucomannan	12 months	56% vs. 29%	27%
Collechia et al.,[50] 2007	307	Open	Rifaximin* plus dietary fibre supplement†	Dietary fibre supplement	24 months	90% vs. 59%	31%

*Rifaximin 400 mg twice daily for 7 days each month for 12 months; †Dietary fibre supplementation of 20g per day.
RCT: Randomised controlled trials.

In the TARGET3 study,[53] in which patients with IBS received repeated courses of rifaximin, susceptibility testing of stool samples before and after each treatment course found no evidence of microbial resistance.

These data confirm the efficacy and safety of rifaximin as long-term cyclic (intermittent) therapy in SUDD. Differences exist as to how and where this can be used. For example, in the USA, rifaximin is licenced for IBS with diarrhoea and so is principally used in IBS patients with SUDD features. In contrast, in European countries it is used mainly in SUDD cases, although it may also have a role in clinically challenging (and non-constipated) IBS patients.

Secondary Prevention of Acute Diverticulitis

The role of mesalamine in prevention of acute diverticulitis recurrence has been extensively evaluated in large RCT, notably the DIVA and the PREVENT1 and PREVENT2 studies.[54,55] In the DIVA study,[54] patients with CT-confirmed acute diverticulitis were randomised to receive standard care plus either mesalamine, mesalamine and a probiotic (*Bifidobacterium infantis* 35624), or placebo for 12 weeks, with efficacy assessed using changes in a composite global symptom score involving 10 key gastrointestinal signs and symptoms. For the primary endpoint, there were no significant differences in recurrence rates between the three groups, although there was some evidence for symptom improvement with mesalamine.[54] In the two PREVENT trials,[55] comparing mesalamine (given for 2 years) with placebo, there were no differences in recurrence rates after 2 years (or in time to recurrence) in the mesalamine and placebo groups in either study. These data support the view that, although mesalamine may have a role in symptomatic treatment, this drug has no benefit in reducing disease recurrence, and this is reflected in the Italian, German, and USA guidelines.[2,6,10]

Studies evaluating the use of probiotics in the treatment and prevention of recurrent diverticulitis are of variable quality and are highly heterogenous regarding study treatments (e.g., probiotic alone or given with mesalamine) and treatment outcomes (although focussing primarily on symptom control).[56-58] While this leads to difficulty in drawing firm conclusions, reported data indicate that the use of probiotics may have some role in symptom management, although, from an evidence-based perspective, no recommendations can be made.

Conclusion

Our understanding of diverticulosis and DD continues to evolve, with notable advances in biology, epidemiology, and therapeutic approaches. The role of rifaximin as a modulator of gut microbiota with potential anti-inflammatory activity holds promise as a therapy in patients with SUDD.

References

1. Scarpignato C et al. Management of colonic diverticular disease in the third millennium: Highlights from a symposium held during the United European Gastroenterology Week 2017. Therap Adv Gastroenterol. 2018;11:1756284818771305.
2. Cuomo R et al. Italian consensus conference for colonic diverticulosis and diverticular disease. United European Gastroenterol J. 2014;2(5):413-42.
3. Cohen E et al. Increased risk for irritable bowel syndrome after acute diverticulitis. Clin Gastroenterol Hepatol. 2013;11(12):1614-9.
4. Andersen JC et al. Danish national guidelines for treatment of diverticular disease. Dan Med J. 2012;59(5):C4453.
5. Andeweg CS et al.; Netherlands Society of Surgery; Working group from Netherlands Societies of Internal Medicine, Gastroenterologists, Radiology, Health Technology Assessment and Dieticians. Guidelines of diagnostics and treatment of acute left-sided colonic diverticulitis. Dig Surg. 2013;30(4-6):278-92.
6. Kruis W et al.; German Society for Gastroenterology, Digestive and Metabolic Diseases and The German Society for General and Visceral Surgery. Diverticular disease: Guidelines of the German Society for Gastroenterology, digestive and metabolic diseases and the German Society for General and Visceral Surgery. Digestion. 2014;90(3): 190-207.
7. Binda GA et al.; Italian Society of Colon and Rectal Surgery. Practice parameters for the treatment of colonic diverticular disease: Italian Society of Colon and Rectal Surgery (SICCR) guidelines. Tech Coloproctol. 2015;19(10):615-26.
8. Pietrzak A et al. Polish

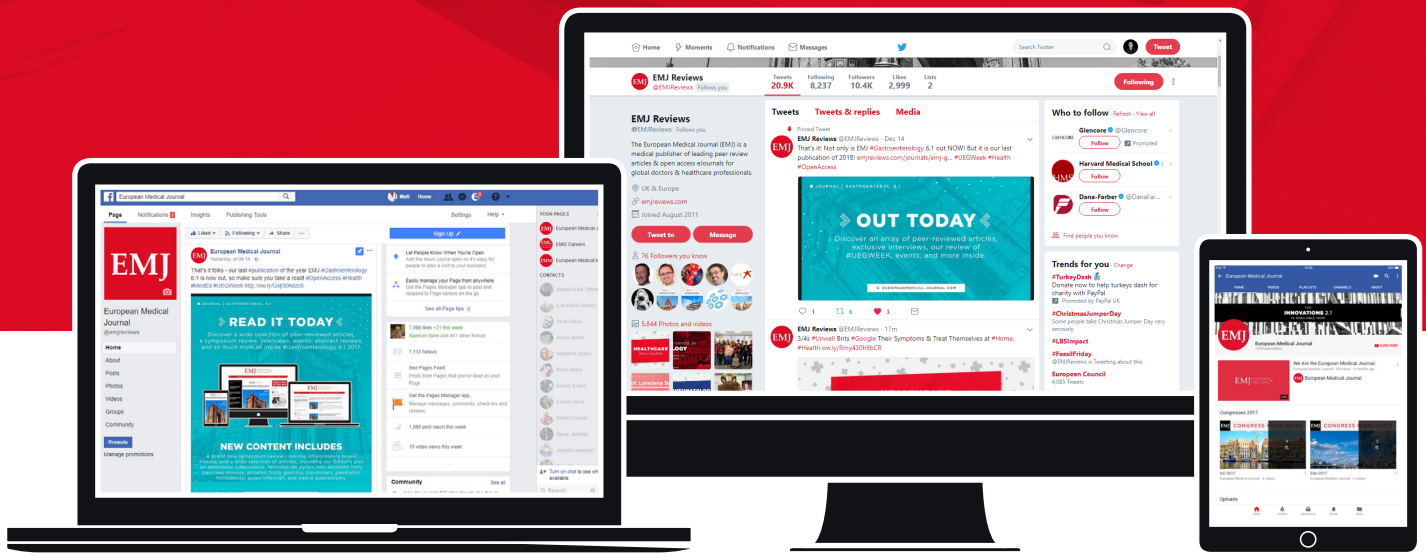
interdisciplinary consensus on diagnostics and treatment of colonic diverticulosis (2015). Pol Przegl Chir. 2015;87(4):203-20.

9. Feingold D et al. Practice parameters for the treatment of sigmoid diverticulitis. Dis Colon Rectum. 2014;57(3):284-94.
10. Stollman N et al.; Committee AGAICG. American Gastroenterological Association Institute Guideline on the Management of Acute Diverticulitis. Gastroenterology. 2015;149(7):1944-9.
11. Murphy T HR et al. World Gastroenterology Organisation Practice Guidelines: Diverticular Disease. 2007. Available at: http://www.worldgastroenterology.org/guidelines/global-guidelines/diverticular-disease/diverticular-disease-english. Last accessed: 13 November 2018.
12. Carabotti M, Annibale B. Treatment of diverticular disease: An update on latest evidence and clinical implications. Drugs Context. 2018;7:212526.
13. Parks TG. Natural history of diverticular disease of the colon. A review of 521 cases. Br Med J. 1969;4(5684):639-42.
14. Weizman AV, Nguyen GC. Diverticular disease: Epidemiology and management. Can J Gastroenterol. 2011;25(7):385-9.
15. Binda GA et al. Trends in hospital admission for acute diverticulitis in Italy from 2008 to 2015. Tech Coloproctol. 2018;22(8):597-604.
16. Cammarota S et al. Increasing trend in admission rates and costs for acute diverticulitis during 2005-2015: Real-life data from the Abruzzo Region. Therap Adv Gastroenterol. 2018;11:1756284818791502.
17. Soh A et al. The increasing prevalence and impact of racial differences on colonic diverticulosis in a multi-ethnic Asian country. P157. 3rd Meeting of the Federation of Neurogastroenterology and Motility and Postgraduate Course on Gastrointestinal Motility (FNM 2018), 29 August-1 September, 2018.
18. Nagata N et al. Alcohol and smoking affect risk of uncomplicated colonic diverticulosis in Japan. PLoS One. 2013;8(12):e81137.
19. Yamada E et al. Association between the location of diverticular disease and the irritable bowel syndrome: A multicenter study in Japan. Am J Gastroenterol. 2014;109(12):1900-5.
20. Mimura T et al. Pathophysiology of diverticular disease. Best Pract Res Clin Gastroenterol. 2002;16(4):563-76.
21. Sugihara K et al. Motility study in right sided diverticular disease of the colon. Gut. 1983;24(12):1130-4.
22. Uno Y, van Velkinburgh JC. Logical hypothesis: Low FODMAP diet to prevent diverticulitis. World J Gastrointest Pharmacol Ther. 2016;7(4):503-12.
23. Barbaro MR et al. Immune activation and nerve sprouting in the colonic mucosa of patients with diverticular disease. OP203. 25th United European Gastroenterology Week, 28 October-1 November, 2017.
24. Humes DJ et al. Visceral hypersensitivity in symptomatic diverticular disease and the role of neuropeptides and low grade inflammation. Neurogastroenterol Motil. 2012;24(4):318-e163.
25. Simpson HL, Campbell BJ. Review article: Dietary fibre-microbiota interactions. Aliment Pharmacol Ther. 2015;42(2):158-79.
26. Tursi A et al. Assessment of fecal microbiota and fecal metabolome in symptomatic uncomplicated diverticular disease of the colon. J Clin Gastroenterol. 2016;50 Suppl 1:S9-12.
27. Kvasnovsky CL et al. Clinical and symptom scores are significantly correlated with fecal microbiota features in patients with symptomatic uncomplicated diverticular disease: A pilot study. Eur J Gastroenterol Hepatol. 2018;30(1):107-12.
28. Daniels L et al. Fecal microbiome analysis as a diagnostic test for diverticulitis. Eur J Clin Microbiol Infect Dis. 2014;33(11):1927-36.
29. Hullar MA et al. The fecal microbiome differentiates patients with a history of diverticulitis vs those with uncomplicated diverticulosis. Gastroenterology. 2017;152 (5 Suppl 1):S624.
30. Barbara G et al. Gut microbiota, metabolome and immune signatures in patients with uncomplicated diverticular disease. Gut. 2017;66(7):1252-61.
31. Jones RB et al. An aberrant microbiota is not strongly associated with incidental colonic diverticulosis. Sci Rep. 2018;8(1):4951.
32. Chabok A et al.; Group AS. Randomized clinical trial of antibiotics in acute uncomplicated diverticulitis. Br J Surg. 2012;99(4):532-9.
33. Daniels L et al. Randomized clinical trial of observational versus antibiotic treatment for a first episode of CT-proven uncomplicated acute diverticulitis. Br J Surg. 2017;104(1):52-61.
34. van Dijk ST et al. Long-term effects of omitting antibiotics in uncomplicated acute diverticulitis. Am J Gastroenterol. 2018;113(7):1045-52.
35. Mocanu V et al. The role of antibiotics in acute uncomplicated diverticulitis: A systematic review and meta-analysis. Am J Surg. 2018;216(3): 604-9.
36. Carabotti M et al. Role of fiber in symptomatic uncomplicated diverticular disease: A systematic review. Nutrients. 2017;9(2):161.
37. Peery AF et al. A high-fiber diet does not protect against asymptomatic diverticulosis. Gastroenterology. 2012;142(2):266-72.e261.
38. Crowe FL et al. Diet and risk of diverticular disease in Oxford cohort of European Prospective Investigation into Cancer and Nutrition (EPIC): Prospective study of British vegetarians and non-vegetarians. BMJ. 2011;343:d4131.
39. Aldoori WH et al. A prospective study of diet and the risk of symptomatic diverticular disease in men. Am J Clin Nutr. 1994;60(5):757-64.
40. Strate LL et al. Western dietary pattern increases, and prudent dietary pattern decreases, risk of incident diverticulitis in a prospective cohort study. Gastroenterology. 2017;152(5):1023-30.
41. Strate LL et al. Nut, corn, and popcorn consumption and the incidence of diverticular disease. JAMA. 2008;300(8):907-14.
42. Maguire LH et al. Higher serum levels of vitamin D are associated with a reduced risk of diverticulitis. Clin Gastroenterol Hepatol. 2013;11(12):1631-5.
43. Cuomo R et al. Rifaximin and diverticular disease: Position paper of the Italian Society of Gastroenterology (SIGE). Dig Liver Dis. 2017;49(6):595-603.
44. Xu D et al. Rifaximin alters intestinal bacteria and prevents stress-induced gut inflammation and visceral hyperalgesia in rats. Gastroenterology. 2014;146(2): 484-96.e484.
45. Ponziani FR et al. Eubiotic properties of rifaximin: Disruption of the traditional concepts in gut microbiota modulation. World J Gastroenterol. 2017;23(25):4491-9.
46. Mencarelli A et al. Inhibition of NF-kappaB by a PXR-dependent pathway mediates counter-regulatory activities of rifaximin on innate immunity in intestinal epithelial cells. Eur J Pharmacol. 2011;668(1-2):317-24.
47. Papi C et al. Efficacy of rifaximin on symptoms of uncomplicated diverticular disease of the colon. A pilot multicentre open trial. Diverticular Disease Study Group. Ital J Gastroenterol. 1992;24(8):452-6.
48. Papi C et al. Efficacy of rifaximin in the treatment of symptomatic diverticular disease of the colon. A multicentre double-blind placebo-controlled trial. Aliment Pharmacol Ther. 1995;9(1):33-9.
49. Latella G et al. Rifaximin improves symptoms of acquired uncomplicated diverticular disease of the colon. Int J

Colorectal Dis. 2003;18(1):55-62.

50. Colecchia A et al. Efficacy of long term cyclic administration of the poorly absorbed antibiotic Rifaximin in symptomatic, uncomplicated colonic diverticular disease. World J Gastroenterol. 2007;13(2):264-9.
51. Bianchi M et al. Meta-analysis: Long-term therapy with rifaximin in the management of uncomplicated diverticular disease. Aliment Pharmacol Ther. 2011;33(8):902-10.
52. Schoenfeld P et al. Safety and tolerability of rifaximin for the treatment of irritable bowel syndrome without constipation: A pooled analysis of randomised, double-blind, placebo-controlled trials. Aliment Pharmacol Ther. 2014;39(10):1161-8.
53. Pimentel M et al. Repeat rifaximin for irritable bowel syndrome: No clinically significant changes in stool microbial antibiotic sensitivity. Dig Dis Sci. 2017;62(9):2455-63.
54. Stollman N et al.; DIVA Investigator Group. A randomized controlled study of mesalamine after acute diverticulitis: Results of the DIVA trial. J Clin Gastroenterol. 2013;47(7):621-9.
55. Raskin JB et al. Mesalamine did not prevent recurrent diverticulitis in Phase 3 controlled trials. Gastroenterology. 2014;147(4):793-802.
56. Fric P, Zavoral M. The effect of non-pathogenic Escherichia coli in symptomatic uncomplicated diverticular disease of the colon. Eur J Gastroenterol Hepatol. 2003;15(3):313-5.
57. Tursi A et al. Mesalazine and/or Lactobacillus casei in preventing recurrence of symptomatic ucomplicated diverticular disease of the colon: A prospective, randomized, open-label study. J Clin Gastroenterol. 2006;40(4):312-6.
58. Tursi A et al. Mesalazine and/or Lactobacillus casei in maintaining long-term remission of symptomatic uncomplicated diverticular disease of the colon. Hepatogastroenterology. 2008;55(84):916-20.

Interact with us on social media.



Join the European Medical Journal community and discover news on the latest healthcare developments.

EUROPEANMEDICAL-JOURNAL.COM

The Emerging Treatment Landscape of Inflammatory Bowel Disease: Role of Innovator Biologics and Biosimilars

This symposium took place on 23rd October 2018, as part of the 26th United European Gastroenterology (UEG) Week in Vienna, Austria

Chairperson: Walter Reinisch[1]

Speakers: Jean-Frédéric Colombel,[2] Walter Reinisch,[1] Alessandro Armuzzi[3]

1. Medical University of Vienna, Vienna, Austria
2. Icahn School of Medicine at Mount Sinai, New York City, New York, USA
3. Gemelli Hospital Catholic University Foundation, Rome, Italy

Disclosure: These disclosures were provided by the faculty for the symposium. Prof Reinisch has been a consultant and an advisory board member for, received lecture fees from, and/or received research grants from 4SC, Abbott Laboratories, AbbVie, Aesca, Amgen, AM Pharma, AOP Orphan, Aptalis, Arena Pharmaceuticals, Astellas, AstraZeneca, Avaxia, Bioclinica, Biogen IDEC, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Cellerix, Celltrion, Centocor, Chemocentryx, Covance, Danone Austria, Elan, Eli Lilly, Ernest & Young, Falk Pharma GmbH, Ferring, Galapagos, Genentech, Gilead, Grünenthal, ICON, Immundiagnostik, Index Pharma, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, LivaNova, Mallinckrodt, Medahead, MedImmune, Millenium, Mitsubishi Tanabe Pharma Corporation, MSD, Nestlé, Nippon Kayaku, Novartis, Ocera, Otsuka, Parexel, PDL, Periconsulting, Pfizer, Pharmacosmos, Philip Morris Institute, PLS Education, Procter & Gamble, Prometheus, Protagonist, Provention, Robarts Clinical Trial, Roland Berger, Sandoz, Schering-Plough, Second Genome, Seres Therapeutics, Setpointmedical, Shire, Sigmoid, Takeda, Therakos, Tigenix, UCB, Vifor, Yakult, Zealand, and Zyngenia. Prof Colombel has been a consultant for AbbVie, Amgen, Boehringer Ingelheim, Celgene Corporation, Celltrion, Eli Lilly, Enterome, Ferring Pharmaceuticals, Genentech, Janssen Pharmaceuticals, MedImmune, Merck, Novartis, Pfizer, Protagonist Therapeutics, Sandoz, Second Genome, Seres Therapeutics, Shire, Takeda, Theradiag, and Theravance Biopharma; received lecture fees from AbbVie, Amgen, Ferring Pharmaceuticals, Shire, and Takeda; received research grants from AbbVie, Janssen, and Takeda; and has stock options in Intestinal Biotech Development and Genfit. Prof Armuzzi has been a consultant for AbbVie, Allergan, Amgen, Biogen, Celgene, Celltrion, Ferring, Hospira, Janssen, Lilly, MSD, Mundipharma, Mylan, Pfizer, Samsung Bioepis, Sandoz, Sofar, and Takeda; received lecture fees from AbbVie, Amgen, AstraZeneca, Chiesi, Ferring, Hospira, Janssen, Medtronic, MSD, Mitsubishi Tanabe, Mundipharma, Nikkiso, Otsuka, Pfizer, Samsung Bioepis, Takeda, Tigenix, and Zambon; and received research grants from MSD, Takeda, and Pfizer.

Acknowledgements: Medical writing assistance was provided by Sam Reed, Elements Communications Ltd., Westerham, UK.

Support: This report summarises presentations given by the speakers at an Amgen Europe-sponsored satellite symposium held at the 26th United European Gastroenterology (UEG) Week in Vienna, Austria on 23rd October 2018. The publication of this article was funded by Amgen. The views and opinions expressed are those of the speakers and not necessarily of Amgen.

Citation: EMJ Gastroenterol. 2018;7[1]:50-57.

Meeting Summary

Despite the fact that the treatment armamentarium for inflammatory bowel diseases (IBD) is growing, unmet medical needs remain. These needs are driven, at least in part, by restricted access to biologics, which means that patients who would benefit from these agents will not receive them. This symposium explored approaches to improve IBD care, evaluating both the potential of novel therapies and the role of optimised treatment using the treat-to-target concept and careful evaluation of use of the right drug at the right time. The reality for clinicians is that selecting the best treatment needs to take into account the best medical option, patient preferences, and cost, which is one of the main barriers limiting access to biologic treatment. In this regard, biosimilars could serve the patient community by facilitating increased access, including use in early intervention to avoid disease progression. Education around biosimilars is essential to ensure patient acceptance of these agents and maximise the opportunity that they provide.

Introduction

Professor Walter Reinisch

Anti-TNF biologics are now well-established standard of care treatments that have significantly improved quality of life and reduced the need for hospitalisation and surgery for patients with IBD. At the same time, novel treatments and therapeutic approaches, which have the potential to further improve patient outcomes, continue to be investigated.[1] While advances in therapy are almost invariably associated with increased costs, the availability of biosimilars offers the opportunity for cost savings, and the potential to increase access to treatment.[2] Prof Reinisch highlighted how the accumulating evidence from recent trials, along with a better understanding of biosimilar development and regulatory approval, have helped to bring about a change in the perception of IBD specialists, such that they now prescribe biosimilars with increased confidence. This is acknowledged in the European Crohn's and Colitis Organisation's (ECCO) updated position statement on biosimilars.[3] The symposium addressed advances both in novel treatments and in biosimilar developments, and for the latter considered the clinicians' and patients' perspectives, which are both important to maximise the potential benefits that can be achieved.

Preparing For the Next Era in the Management of Inflammatory Bowel Diseases

Professor Jean-Frédéric Colombel

Prof Colombel noted that the incidence of IBD continues to increase steadily in Western countries and more dramatically in newly industrialised countries, such as China and India.[4] However, despite discussions around the best treatment options, cost remains a barrier to biologic therapies, which can lead to restricted access and suboptimal treatment strategies. A report by Siegel et al.[5] highlighted real-world evidence from the USA indicating that, from January 2008–March 2016, only a small proportion of patients (<5%) received biologic therapeutics. In contrast, approximately 30% of IBD patients initially received treatment with 5-aminosalicylic acid (5-ASA), which is not approved for Crohn's disease (CD) in the USA, and many continued to receive this agent during the treatment pathway.[5] Three broad approaches were discussed to address unmet needs in IBD: improving current care, searching for a cure, and exploring prevention strategies (Table 1).

Table 1: Approaches to address unmet needs in inflammatory bowel disease treatment.

Improving care	Looking for a cure	Exploring prevention
› Early intervention. › Treat-to-target. › Tight control.	› Profiling to better understand disease mechanisms. › Correcting underlying defective pathways.	› Improving understanding of the preclinical phase of inflammatory bowel disease. › Predicting disease based on serological markers prior to the first symptoms.

Early intervention with biologics, treat-to-target, and tight control of clinical symptoms and biomarkers are essential for optimising current IBD care. The importance of early intervention was highlighted in a recent study of 130 patients with CD: while bowel damage increased with disease duration, damage was reduced in patients who received anti-TNF therapy within the first 2 years of disease progression compared with those exposed later.[6] A treat-to-target approach focusses on achieving remission or low disease activity using evidence-based treatment targets. This involves patients and clinicians agreeing strict definitions for treatment targets and working towards achieving them by adopting changes in therapy within distinct time frames.[7] The current target is clinical remission of symptoms and mucosal healing.[7] Tight control involves treatment decisions based on regular monitoring of intestinal inflammatory biomarkers, such as C-reactive protein (CRP) and faecal calprotectin, and clinical symptoms.[8] The benefits of tight control of disease activity are illustrated by results from studies such as CALM,[9] an open-label, randomised, controlled Phase III study of patients with active endoscopic CD. Adalimumab initiation, escalation, and de-escalation, driven by monitoring a combination of CRP and faecal calprotectin biomarkers, Crohn's Disease Activity Index (CDAI), and prednisone use, led to improvements in the rate of mucosal healing and an absence of deep ulcerations 48 weeks after randomisation, compared with clinical management using escalation, based on CDAI and prednisone use alone.

While novel treatments have provided further benefits to patients, the efficacy of these drugs, such as ustekinumab, is beginning to plateau during maintenance treatment[10] and there is a need to find alternative approaches. Promising new drugs to treat IBD include additional JAK inhibitors (such as tofacitinib, which is already approved for ulcerative colitis [UC] in Europe)[11] and the sphingosine 1-phosphate receptor modulator class.[12] There is also growing interest in novel approaches to combine biologics in IBD therapy, for example, using adalimumab in combination with vedolizumab,[13] and the cost savings associated with biosimilar treatment may help support such an approach. Future treatment strategies are anticipated to include personalised medicine approaches and the increasing use of diagnostic and predictive biomarkers. For example, a recent publication by West et al.[14] demonstrated that low pretreatment oncostatin M levels compared with higher levels of the protein in the mucosa were associated with improved complete mucosal healing following infliximab therapy in patients with IBD.

The concepts of 'cure' and 'prevention' in IBD were explored during the symposium. It was noted that understanding the mechanisms underlying IBD in an individual is crucial, and this includes the genetic, microbial, immunological, and metabolomic profiles and the clinical phenotype. Genetic analysis may be useful for identifying the causes of IBD and offering the patient appropriate treatment aimed at correcting the defective pathway. This was illustrated by the case of an early-onset IBD patient with a homozygous mutation in an IL-10 receptor (IL10R2) who had disease remission following allogeneic stem cell transplantation from a sibling with a normal *IL10R2* gene.[15] However, given the genetic complexities of IBD,[15] a cure is unlikely to be reached in the near future. Consequently, effective disease prevention, through an improved understanding of the preclinical

phase of disease, is essential. During this phase, environmental and genetic factors interact and result in initiation and propagation of disease followed by subclinical inflammation and tissue damage.[16] Increasing evidence demonstrates that this preclinical period, in which immunological changes in inflammatory markers and antimicrobial antibodies can be detected, can occur years before IBD diagnosis.[17] A serological tool has recently been developed, using microbial antibodies and proteomic markers, that can predict CD around 5 years before the first symptoms.[18] Gaining further insight into this preclinical phase of IBD could pave the way for preventative strategies.

Prof Colombel concluded his presentation by summarising that IBD are progressive, complex, heterogeneous diseases, the importance of optimising current treatments, and how disease prediction and prevention are likely to be central for the future of IBD management.

Upcoming Biosimilars in the Spotlight: What to Consider When Selecting

Professor Walter Reinisch

The anti-TNF biologics infliximab and adalimumab are effective and established treatments for adult and paediatric CD and UC patients. Biosimilars of these agents are now available in Europe, adding to the range of potential treatment options (Table 2).[11,19] Prof Reinisch provided an overview of the anti-TNF agents available and discussed some of the key factors that clinicians should consider when evaluating them for use in the clinic.

The totality of evidence is the data package generated for a biosimilar to demonstrate that it is equivalent to the reference product. This focusses on analytical and functional analyses of the biosimilar supported by data from clinical studies. For biosimilars, guidelines suggest that only one confirmatory trial is generally required, and clinical studies are designed to demonstrate that there are no clinically meaningful differences compared with the reference product rather than efficacy and safety per se. Biosimilar clinical studies are usually equivalence trials and the most sensitive patient populations and clinical endpoints should be identified to ensure that any differences between the biosimilar and reference product with respect to efficacy, safety, and immunogenicity can be attributed to product characteristics rather than patient and disease-related factors.[20,21] Adalimumab biosimilars have primarily been evaluated in Phase III trials of moderate-to-severe plaque psoriasis (PsO) and/or rheumatoid arthritis (RA). In PsO, there is a relatively high placebo-adjusted response rate. This, combined with the fact that biologics are not usually administered with immunosuppressive therapy, facilitates the detection of small differences in efficacy, safety, and immunogenicity. However, assessment in RA does allow for comparison between biosimilar and reference product in combination with standard of care immunosuppressive agents.[22] Evaluating biosimilars in IBD models is difficult because of the high inter-individual variability in pharmacokinetics and because surrogate markers, such as therapeutic drug monitoring, are required to assess systemic inflammation. Patients with IBD also display heightened immune responses that can lead to accelerated drug clearance relative to other populations.[23] The use of biosimilars is, therefore, generally extrapolated to the IBD population at the time of licensing.

Data supporting switching from reference product to biosimilar are important to provide confidence in continued efficacy, safety, and immunogenicity. Because all biosimilars are unique, data on switching should be assessed for each agent. Switching data for the adalimumab biosimilar ABP 501 were discussed during the symposium as an example of the data that may be generated. Equivalence of ABP 501 and the adalimumab reference product has been demonstrated in terms of efficacy, safety, and immunogenicity in two Phase III, randomised controlled equivalence trials: one in moderate-to-severe PsO (N=350)[24,25] and one in moderate-to-severe RA (N=526).[26] In the 52-week Phase III PsO trial, a switch occurred at Week 16, with patients who were initially randomised to the adalimumab reference product arm being re-randomised to continue on the reference product or to receive ABP 501.

Table 2: Approved adalimumab and infliximab biosimilars in Europe and the USA (November 2018).[11,19]

Company	Biosimilar	Reference product	EC approval	FDA approval
Celltrion Healthcare/Pfizer	CT-P13 (two biosimilar brands)	Infliximab	September 2013	April 2016
Samsung Bioepis/Biogen	SB2	Infliximab	May 2016	April 2017
Amgen	ABP 501	Adalimumab	March 2017	September 2016
Samsung Bioepis/Biogen	SB5	Adalimumab	August 2017	Not yet obtained
Boehringer Ingelheim	BI 695501	Adalimumab	November 2017	August 2017
Sandoz/Pfizer	PF-06438179 (two biosimilar brands)	Infliximab	May 2018	December 2017
Sandoz	GP2017 (three biosimilar brands)	Adalimumab	July 2018	October 2018
Mylan/Fujifilm	FKB327	Adalimumab	September 2018	Not yet obtained

EC: European Commission; FDA: U.S. Food and Drug Administration.

Patients treated with ABP 501 and adalimumab reference product had similar clinical efficacy, safety, and immunogenicity profiles over the duration of the trial, including after the single switch.[24,25] In RA, a 26-week Phase III parent study[26] was followed by a 72-week, open-label extension study[27] (i.e., total duration of 98 weeks), in which all eligible patients, including those initially receiving adalimumab reference product, could continue on ABP 501. In the open-label extension study, efficacy, safety, and immunogenicity were comparable to those seen in the parent study.[27-29] The formulation may be an important consideration when evaluating different adalimumab biosimilars, as injection-site pain can impact patient acceptance of treatment. It was noted that patients receiving ABP 501, which is citrate-free, reported lower injection-related pain compared with the citrate-containing adalimumab reference product in both the Phase III PsO and RA trials.[30]

As clinical data in IBD have not been included in the regulatory submissions of adalimumab biosimilars approved to date, the use of these agents in these indications currently relies on extrapolation. Extrapolation of clinical efficacy and safety data to other indications of the reference product, not studied in clinical trials for the biosimilar, is fundamental to the concept of biosimilars. Extrapolation is possible and should be considered in light of the totality of evidence for a biosimilar (the analytical, functional [including mechanism of action], and the clinical and non-clinical data) along with adequate scientific justification. Additional data may be required to support extrapolation when it is not clear whether the efficacy and safety reported in one indication are relevant for another indication.[20,31]

Prof Reinisch summarised his presentation by explaining that clinicians need to be aware of the many considerations when selecting a biosimilar in order to reach a fully informed decision.

Alleviating Patient Concerns About Biosimilars: Challenges and Opportunities

Professor Alessandro Armuzzi

A comparison of surveys among IBD specialists performed in 2013 and 2015 highlighted that clinicians have become better informed about biosimilars and more confident in their use in clinical practice.[32] However, this increased confidence is not always mirrored in patients. As a consequence, Prof Armuzzi explained the importance of ensuring that patients are well informed to maximise both the acceptance and clinical benefits of these agents.

The results of a survey conducted by the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA),[33] which evaluated patient (N=1,181) perceptions of biosimilars, were discussed during the symposium. Some patients were found to have concerns about biosimilars, particularly around efficacy, safety, and extrapolation to IBD, and wanted to know what biologic they were receiving (i.e., biosimilar or reference product). Overall, these findings highlight that patients with IBD require more information about biosimilars, and that they should be fully informed and involved in the treatment decision-making process. Increasing confidence in biosimilars and empowering patients can be facilitated by educating patients about the data supporting equivalence of a biosimilar to the reference product. For example, the totality of evidence concept should be explained, emphasising that the mechanism of action is the same between a biosimilar and reference product and that the extent of both analytical and functional data goes beyond a single clinical trial. Explaining these concepts to patients in a simple manner may help to improve their understanding of and confidence in biosimilars.

A considerable body of data from many fields of research has linked negative patient expectations to the occurrence of adverse symptoms and/or lack of efficacy, in turn impacting wellbeing of patients and treatment adherence. Such data suggest that a nocebo effect associated with a therapeutic intervention may be possible; the nocebo effect has subsequently been defined as an effect that is unrelated to the physiological action of the treatment and arises as a result of the psychosocial context or therapeutic environment on the patient's mind, body, and brain.[34] The potential for the nocebo effect has been reported in association with biosimilars.[35] The underlying causes of the nocebo effect are complex and incompletely understood; some risk factors, such as clinical characteristics and symptom expectations, are pre-existing in the patient, whereas others can be acquired (e.g., through verbal suggestions).[35] The importance of expectation in the context of the nocebo effect was discussed using the example of the opioid analgesic remifentanil. Expectation of a positive treatment outcome doubled the analgesic effect of the drug, whereas expectation of a negative outcome eliminated the analgesic effect.[36]

Given the potential risk of the nocebo effect when switching patients to biosimilars, clinicians should be familiar with strategies to prevent and manage its occurrence. At the heart of this lies communication between clinicians and patients. The BIO-SWITCH study[37] evaluated the efficacy and safety of switching from infliximab reference product to CT-P13 in patients (N=192) with RA, psoriatic arthritis, or ankylosing spondylitis over a 6-month follow-up period. In this study, all patients received a letter about the option to transition to CT-P13 and a subsequent telephone follow-up; treatment was administered in group intravenous sessions. During this study, 24% of patients discontinued CT-P13, mainly due to subjective complaints that could possibly be explained by the nocebo effect. The BIO-SPAN study[38] of patients (n=625) who underwent a non-mandatory switch from reference product to biosimilar etanercept used an enhanced structured communication approach. This involved a letter to patients about switching with a telephone follow-up and treatment was administered in individual subcutaneous sessions. Furthermore, the reduced costs associated with biosimilars were highlighted to patients, and healthcare professionals received soft skills training on potential objection handling and approaches to avoid the nocebo effect.[38,39] A similar 6-month treatment persistence rate was observed following the switch compared with etanercept-treated patients in an historical cohort (N=600).[38] Thus, good communication and education could have an effect on minimising the occurrence of the nocebo effect in combination with other approaches, such as building a strong clinician–patient relationship and identifying patients at risk (Figure 1).[35,40,41]

Prof Armuzzi concluded by explaining that several different communication strategies should be explored to prevent and manage the nocebo effect. These should include patient education and involve not just patients and clinicians but also other healthcare professionals, such as nurses, who play an important role in conveying information about biosimilars to patients.[40]

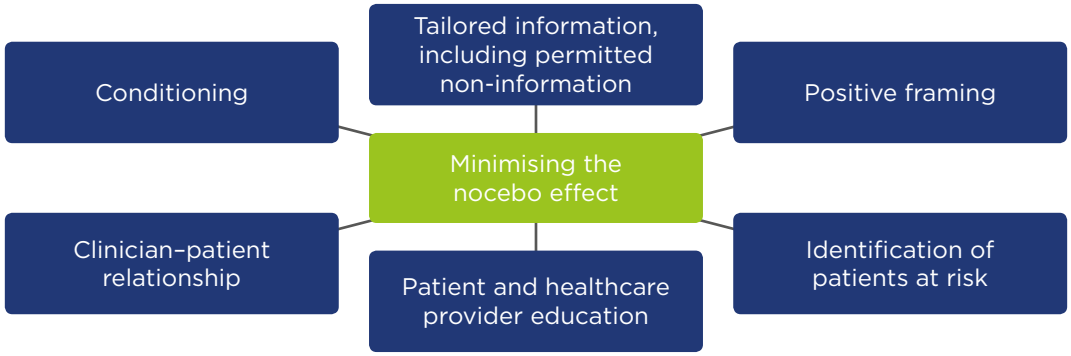


Figure 1: Strategies to minimise the occurrence of the nocebo effect.

Adapted from Armuzzi et al.[40] and Kristensen et al.[41]

Concluding Remarks

Optimising the current management of IBD and developing strategies to predict and prevent IBD at the preclinical stage of disease are key elements in the evolving treatment landscape. Biosimilars of adalimumab are anticipated to play an important role in improving current care by providing cost savings and facilitating access to treatment. Clinicians should carefully consider the multitude of factors when selecting biosimilars, including the available totality of evidence, and should ensure that patients are informed, engaged, and empowered about their treatment through the use of effective communication strategies.

TO VIEW THE WEBCAST OF THE SYMPOSIUM, PLEASE CLICK ON THE LINK BELOW ←

ENTER THE PASSWORD 'UEGWVienna' WHEN PROMPTED

https://vimeo.com/302810410

References

1. Lee HS et al. Novel treatments for inflammatory bowel disease. Korean J Intern Med. 2018;33(1):20-7.
2. Zheng MK et al. Insights on the use of biosimilars in the treatment of inflammatory bowel disease. World J Gastroenterol. 2017;23(11):1932-43.
3. Danese S et al. ECCO position statement on the use of biosimilars for inflammatory bowel disease – An update. J Crohns Colitis. 2017;11(1): 26-34.
4. Kaplan GG, Ng SC. Understanding and preventing the global increase of inflammatory bowel disease. Gastroenterology. 2017;152(2):313-21.
5. Siegel C et al. Real-world treatment pathway visualizations show low use of biologic therapies in Crohn's disease and ulcerative colitis in the United States. Abstract DOP060. European Crohn's and Colitis Organisation (ECCO) Congress, 15-18 February, 2017.
6. Farre C et al. Correlation between the Lemann Index and the Inflammatory Bowel Disease-Disability Index in Crohn's disease. Abstract P187. European Crohn's and Colitis Organisation (ECCO) Congress, 14-17 February, 2018.
7. Peyrin-Biroulet L et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): Determining therapeutic goals for treat-to-target. Am J Gastroenterol. 2015;110(9): 1324-38.
8. Colombel JF et al. Management strategies to improve outcomes of patients with inflammatory bowel diseases. Gastroenterology. 2017;152(2):351-61.
9. Colombel JF et al. Effect of tight control management on Crohn's disease (CALM): A multicentre, randomised, controlled Phase 3 trial. Lancet. 2018;390(10114):2779-89.
10. Ungaro RC et al. Net remission rates with biologic treatment in Crohn's disease: A reappraisal of the clinical trial data adjusting for both induction and remission phases and prior exposure to TNF antagonists. Abstract Sa1759. Digestive Disease Week, 2-5 June, 2018.
11. EMA. Authorised medicines. Available at: https://www.ema.europa.eu/en/medicines. Last accessed: 12 November 2018.
12. Hindryckx P et al. The expanding therapeutic armamentarium for inflammatory bowel disease: How to choose the right drug[s] for our patients? J Crohns Colitis. 2018;12(1):105-19.
13. Hirten RP et al. Combining biologics

in inflammatory bowel disease and other immune mediated inflammatory disorders. Clin Gastroenterol Hepatol. 2018;16(9):1374-84.

14. West NR et al. Oncostatin M drives intestinal inflammation and predicts response to tumor necrosis factor-neutralizing therapy in patients with inflammatory bowel disease. Nat Med. 2017;23(5):579-89. Erratum in: Nat Med. 2017;23(6):788.
15. Glocker EO et al. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. N Engl J Med. 2009;361(21):2033-45.
16. Torres J et al. Preclinical disease and preventive strategies in IBD: Perspectives, challenges and opportunities. Gut. 2016;65(7):1061-9.
17. Torres J et al. Evidence for life before inflammatory bowel disease. Clin Gastroenterol Hepatol. 2016;14(6):825-8.
18. Choung RS et al.; PREDICTS Study Team. Serologic microbial associated markers can predict Crohn's disease behaviour years before disease diagnosis. Aliment Pharmacol Ther. 2016;43(12):1300-10.
19. FDA. Approved drug products. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/. Last accessed: 12 November 2018.
20. EMA. Similar biological medicinal products containing monoclonal antibodies: Non-clinical and clinical issues. 2012. Available at: https://www.ema.europa.eu/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-monoclonal-antibodies-non-clinical_en.pdf. Last accessed: 12 November 2018.
21. FDA. Scientific considerations in demonstrating biosimilarity to a reference product. Guidance for industry. 2015. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Last accessed: 12 November 2018.
22. Lai Z, La Noce A. Key design considerations on comparative clinical efficacy studies for biosimilars: Adalimumab as an example. RMD Open. 2016;2(1):e000154.
23. Altwegg R, Vincent T. TNF blocking therapies and immunomonitoring in patients with inflammatory bowel disease. Mediators Inflamm. 2014;2014:172821.
24. Papp K et al. Clinical similarity of biosimilar ABP 501 to adalimumab in the treatment of patients with moderate to severe plaque psoriasis: A randomized, double-blind, multicenter, Phase III study. J Am Acad Dermatol. 2017;76(6):1093-102.
25. Papp K et al. Clinical similarity of the biosimilar ABP 501 compared with adalimumab after single transition: Long-term results from a randomized controlled, double-blind, 52-week, Phase III trial in patients with moderate-to-severe plaque psoriasis. Br J Dermatol. 2017;177(6):1562-74.
26. Cohen S et al. Efficacy and safety of the biosimilar ABP 501 compared with adalimumab in patients with moderate to severe rheumatoid arthritis: A randomised, double-blind, Phase III equivalence study. Ann Rheum Dis. 2017;76(10):1679-87.
27. Cohen S et al. ABP 501 biosimilar to adalimumab: Final safety, immunogenicity, and efficacy results from an open-label extension study. Poster SAT0171. European League Against Rheumatism (EULAR) Annual Congress, 14-17 June, 2017.
28. Krishnan E et al. Two-year consolidated safety data for ABP 501 in patients with moderate to severe rheumatoid arthritis. Poster SAT0180. European League Against Rheumatism (EULAR) Annual Congress, 13-16 June, 2018.
29. Krishnan E et al. Immunogenicity associated with a transition from adalimumab reference product to ABP 501 in patients with rheumatoid arthritis. Poster THU0198. European League Against Rheumatism (EULAR) Annual Congress, 13-16 June, 2018.
30. Krishnan E et al. Indirect standardised assessment of injection site pain following subcutaneous administration of citrate-free formulation of adalimumab and its biosimilar ABP 501. Poster FRI0115. European League Against Rheumatism (EULAR) Annual Congress, 13-16 June, 2018.
31. EMA. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Non-clinical and clinical issues. 2014. Available at: https://www.ema.europa.eu/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-2.pdf. Last accessed: 12 November 2018.
32. Danese S et al. Changes in biosimilar knowledge among European Crohn's Colitis Organization [ECCO] Members: An updated survey. J Crohns Colitis. 2016;10(11):1362-5.
33. Peyrin-Biroulet L et al. Patient perspectives on biosimilars: A survey by the European Federation of Crohn's and Ulcerative Colitis Associations. J Crohns Colitis. 2017;11(1):128-33.
34. Colloca L, Finniss D. Nocebo effects, patient-clinician communication, and therapeutic outcomes. JAMA. 2012;307(6):567-8.
35. Pouillon L et al. The nocebo effect: A clinical challenge in the era of biosimilars. Expert Rev Clin Immunol. 2018;14(9):739-49.
36. Bingel U et al. The effect of treatment expectation on drug efficacy: Imaging the analgesic benefit of the opioid remifentanil. Sci Transl Med. 2011;3(70):70ra14.
37. Tweehuysen L et al. Subjective complaints as the main reason for biosimilar discontinuation after open-label transition from reference infliximab to biosimilar infliximab. Arthritis Rheumatol. 2018;70(1):60-8.
38. Tweehuysen L et al. Open-label, non-mandatory transitioning from originator etanercept to biosimilar SB4: Six-month results from a controlled cohort study. Arthritis Rheumatol. 2018;70(9):1408-18.
39. Tweehuysen L et al. Higher acceptance and persistence rates after biosimilar transitioning in patients with a rheumatic disease after employing an enhanced communication strategy. Abstract FRI0200. European League Against Rheumatism (EULAR) Annual Congress, 14-17 June, 2017.
40. Armuzzi A et al. Nurses are critical in aiding patients transitioning to biosimilars in inflammatory bowel disease: Education and communication strategies. J Crohns Colitis. 2018. [Epub ahead of print].
41. Kristensen LE et al. Non-pharmacological effects in switching medication: The nocebo effect in switching from originator to biosimilar agent. BioDrugs. 2018;32(5):397-404.

Are We Ready to Change the Course of Inflammatory Bowel Disease?

This symposium took place on 22nd October 2018, as part of the 26th United European Gastroenterology (UEG) Week in Vienna, Austria

Chairperson: Remo Panaccione[1]

Speakers: Laurent Peyrin-Biroulet,[2] Jean-Frédéric Colombel,[3] Edouard Louis[4]

1. University of Calgary, Calgary, Canada
2. Nancy University Hospital, Nancy, France
3. Icahn School of Medicine at Mount Sinai, New York City, New York, USA
4. Liège University Hospital, Liège, Belgium

Disclosure: Prof Panaccione has received consulting and/or speaking and/or advisory board fees, and/or research/educational support from AbbVie, Abbott, ActoGeniX, AGI Therapeutics, Alba Therapeutics Albireo, Alfa Wasserman, Amgen, AM-Pharma BV, Anaphore, Aptalis, Astellas, AstraZeneca, Athersys, Atlantic Healthcare, Baxter, BioBalance, Biogen Idec, Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, Celek, Cellerix, Cerimon, ChemoCentryx, CoMentis, Cosmo Technologies, Coronado Biosciences, Cubist, Cytokine Pharmasciences, Eagle, Eisai Medical Research, Elan, EnGene, Eli Lilly, Enteromedics, Exagen Diagnostics, Ferring, Flexion Therapeutics, Funxional Therapeutics, Genentech, Genzyme, Gilead, Given Imaging, GlaxoSmithKline, Hospira, Human Genome Sciences, Ironwood, Janssen, KaloBios, Lexicon, Lycera, Meda, Merck & Co., Merck Research Laboratories, Merck Serono, Millennium, Nisshin Kyorin, Novo Nordisk, NPS Pharmaceuticals, Optimer, Orexigen, PDL Biopharma, Pfizer, Procter and Gamble, Prometheus Laboratories, ProtAb, Purgenesis Technologies, Receptos, Relypsa, Salient, Salix, Santarus, Shire Pharmaceuticals, Sigmoid Pharma, Sirtris (a GSK company), S.L.A. Pharma (UK), Takeda, Targacept, Teva, Therakos, Tillotts, TxCell SA, UCB Pharma, Vascular Biogenics, Viamet, and Warner Chilcott UK. Prof Peyrin-Biroulet has received consulting and/or lecture fees from AbbVie, Amgen, Biogaran, Biogen, Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, Celltrion, Ferring, Forward Pharma, Genentech, H.A.C. Pharma, Hospira, Index Pharmaceuticals, Janssen, Lycera, Merck, Lilly, Mitsubishi, Norgine, Pfizer, Pharmacosmos, Pilège, Samsung Bioepis, Sandoz, Takeda, Therakos, Tillots, UCB Pharma, and Vifor. Prof Colombel has received consulting and/or speaking fees and/or research grants from AbbVie, Amgen, Boehringer-Ingelheim, Celgene Corporation, Celltrion, Enterome, Ferring Pharmaceuticals, Genentech, Janssen Pharmaceuticals, Eli Lilly, Medimmune, Merck & Co., Novartis, Pfizer, Protagonist Therapeutics, Sandoz, Second Genome, Seres Therapeutics, Shire, Takeda, Theradiag, and Theravance Biopharma. He has stock options in Intestinal Biotech Development, and Genfit. Prof Louis has served as a speaker or consultant, and/or on the advisory board for Abbott, AbbVie, AstraZeneca, Celltrion, Celgene, Ferring, MSD, Chiesi, Falk, Takeda, Hospira, Janssen, Pfizer, and Mitsubishi Pharma. He has received funding from AbbVie, MSD, Pfizer, and Takeda.

Acknowledgements: Writing assistance was provided by Helen Saul.

Support: The symposium and this article were funded by AbbVie Ltd.

Citation: EMJ Gastroenterol. 2018;7[1]:58-66.

Meeting Summary

The objectives of the symposium were to raise awareness of the importance of treating early, setting treatment goals, and using enhanced clinical monitoring in inflammatory bowel disease (IBD). The progressive nature of Crohn's disease (CD) leading to bowel damage is well-established, but, according to Prof Peyrin-Biroulet, there may be a window of opportunity early in the disease when progression can be prevented through early diagnosis coupled with early intervention. The same approach should be adopted for the treatment of ulcerative colitis (UC), which he noted is frequently undertreated. UC is also progressive and the overall disability associated with UC is similar to CD.

Prof Colombel described the treat to target (T2T), with tight control (TC), approach in IBD. The target is a composite endpoint of clinical and endoscopic remission, determined and agreed upon with the patient. In this approach, the disease is continuously monitored and treatment modified until the target is reached with the primary aim of blocking disease progression. The CALM study[1] demonstrated that a significantly higher proportion of patients in the TC arm achieved mucosal healing at 1 year compared to patients with a conventional treatment management. In order to illustrate the benefits of early diagnosis, Prof Panaccione presented two cases from clinical practice who exhibited similar symptoms at disease onset. The first case took 3 years to present; her treatment was managed conventionally and escalated according to symptoms with no assessment of biomarkers. She had recurrent symptoms and eventually required ileocaecal resection. By contrast, in the second case, diagnosis occurred within 4 months of symptom onset, and biomarkers were assessed. Biological treatment was initiated at the second consultation and optimised with a TC approach. The treatments in both cases were similar; however, conventional management resulted in disease progression and the T2T approach with TC resulted in asymptomatic, full disease control.

Prof Louis emphasised that good communication between physicians and patients results in the development of goals that are both relevant and meaningful to patients. Patient-reported outcomes (PRO) are increasingly included in clinical trials and required by regulatory agencies. Prof Louis described how tools such as the IBD Disk, which was developed in partnership with patients, can highlight issues that impact the patient's life and therefore aid in optimal communication between physicians and patients.

Symposium Introduction

Professor Remo Panaccione

It is well established that CD is a progressive disease; however, the progressive nature of UC is less widely accepted. The objective of the symposium was to increase awareness of the progressive nature of UC and the importance of treating early, setting treatment goals, and using enhanced clinical monitoring. Additionally, the symposium aimed to highlight the importance of the patient's perspective beyond their symptoms in order to improve communication with patients on the impact of IBD and its treatment on the broader aspects of quality of life.

Assessing the Course: Understanding Progression in Inflammatory Bowel Disease

Professor Laurent Peyrin-Biroulet

For almost a century, it has been established that IBD is associated with permanent damage to the bowel. In the early 1930s, Burril B. Crohn first described[2] the strictures, multiple fistula, disease progression, and bowel damage in regional ileitis, now known as CD, but it took decades for the progressive nature of CD to be fully understood. Prof Peyrin-Biroulet outlined the findings of studies that demontrated the progressive nature of CD. A population-based cohort study[3] in 2010 found 18.6% of CD patients experienced penetrating or stricturing complications within 90 days of diagnosis.

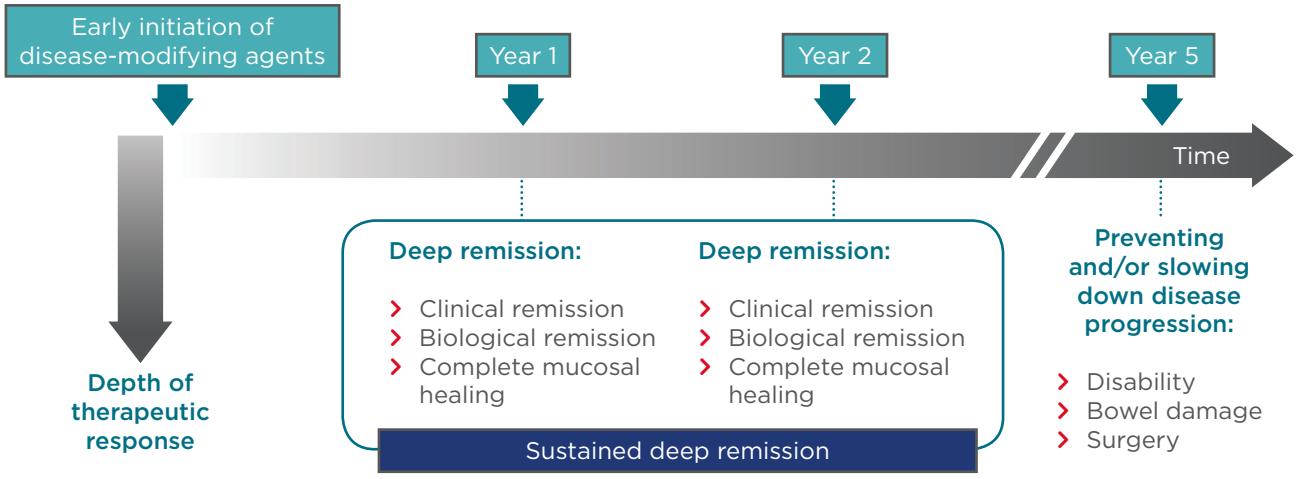


Figure 1: Targeting early Crohn's disease and achieving sustained deep remission: The best way to change disease course?

The aim of initiating treatment early with disease-modifying agents is to achieve and sustain deep remission; it is not enough to achieve deep remission once. The aim of this treatment approach is to improve disease outcomes in the long-term, as result of slowing down or preventing disease progression.

Adapted from Peyrin-Biroulet et al.[8] and Bouguen et al.[9]

The cumulative risk of developing either complication was 33.7% at 5 years and 50.8% 20 years after diagnosis. More recent research suggests that the percentage of patients with bowel damage at diagnosis could be even higher. Using cross-sectional imaging, a joint French–Italian group found that 39.4% of patients had bowel damage at diagnosis;[4] complications included fistulas, strictures, and abscesses. Bowel damage at diagnosis was associated with a worse prognosis than non-stricturing and non-penetrating disease.[4] After a median follow-up of 4.9 years, patients with complicated CD (i.e., bowel damage at diagnosis [n=56]) were significantly more likely to have had intestinal surgery (hazard ratio [HR]: 3.21; p<0.001) and CD-related hospitalisation (HR: 1.88; p<0.002) than those with early-diagnosed CD and no damage (n=86).[4] According to Prof Peyrin-Biroulet, such data highlight how one goal of early diagnosis and disease control is to prevent surgery in the long-term.

Drawing on his personal experience, Prof Peyrin-Biroulet suggested that patients can be disappointed by surgical outcomes. Progression in IBD may start with stricture followed by fistula or abscess and the need for surgery. However, a few weeks following surgery, another stricture may occur, and the process may begin again. Prof Peyrin-Biroulet suggested there is a possible window of opportunity early in the course of the disease when progression may be prevented and, thus, early diagnosis coupled with early intervention could result in better disease control.[5]

The primary benefit of earlier diagnosis and intervention is that anti-TNF therapy may be more effective when used early in the course of CD progression.[6] A pooled analysis[6] of patients taking adalimumab found that remission rates (measured as Crohn's Disease Activity Index [CDAI] <150 or Harvey–Bradshaw index <5) were significantly higher in patients with a disease course of <2 years compared with patients who had had CD for >5 years before initiating treatment. Similar results were found in the exploratory analysis of the EXTEND study.[7] Of the patients receiving continuous adalimumab (40 mg every other week [EOW]), 33% of patients with early CD (≤2 years) were in deep remission (absence of mucosal ulceration and CDAI <150) at Week 52. Only 16% of patients with a disease duration >5 years experienced deep remission. Prof Peyrin-Biroulet noted that if anti-TNF therapy is introduced soon after diagnosis, the probability of achieving full remission, as assessed by both CDAI and mucosal healing data, is greater.

The key concept in CD management for the next decade will be the importance of the window of opportunity early in disease course when treatment with disease-modifying agents can lead to early and sustained deep remission. As outlined in Figure 1,[9] the goal of treatment is to achieve deep remission, including biological and clinical remission and complete mucosal healing, at every evaluation. Data from the CALM study[1] suggest that this approach may prevent, or at least impede, disease progression so that CD patients have decreased disability, reduced bowel damage, and are less likely to require surgery.

The same approach needs to be adopted in UC. Patients with UC are often undertreated because of perceptions that colectomy is a cure, that UC disease burden is less than the burden associated with CD, and that UC is not a progressive disease. However, these are misperceptions, according to Prof Peyrin-Biroulet. While colectomy is an option in UC and is sometimes necessary or a good option when disease complications, such as strictures, malignancy, or dysplasia occur, colectomy is not always a cure. In the postoperative short term (≤30 days), 21% of patients with UC will develop some complication.[10] In the long-term (>30 days), 39% of patients have complications, such as pouchitis (29%), faecal incontinence (21%), small bowel obstruction (17%), fistula (6%), and even mortality (1% in the short term, 0.2% in the long term).[10]

In terms of disease burden and overall disability, UC and CD have been shown to have a similar impact on patients.[11] A study using a quality of life questionnaire assessing fatigue and work productivity among other factors found that the score on the IBD-disability index was 33.9±19.5 for patients with CD (n=150) and 39.2±23.1 for those with UC (n=50).[11]

With regard to the progressive nature of UC, the extent of colorectal inflammation changes over time and structural changes, such as strictures, pseudopolyposis, and bridging fibrosis, are associated with UC.[12] Prof Peyrin-Brioulet also noted that functional abnormalities (decreased contractility and motility, impaired colonic permeability) and anorectal dysfunction ('lead pipe' colon, rectal narrowing, and widening of presacral space[12]) will damage patients' quality of life.

Furthermore, colonic strictures should raise concerns about the risk of cancer. A nationwide study from GETAID included patients without preoperative evidence of dysplasia or cancer who underwent surgery for colonic strictures. Of 12,013 patients who underwent surgery between 1992 and 2014, 248 patients with CD and 39 patients with UC had low or high-grade dysplasia or cancer.[13] Prof Peyrin-Biroulet highlighted that dysplasia and cancer are associated with undertreated disease.

In conclusion, both UC and CD are progressive diseases. The disease burden depends on many factors but is broadly similar in UC and CD. Early intervention and disease control are necessary also in UC to improve short and long term outcomes and to avoid disability and colectomy.

Navigating Outcomes: Optimising Treatment of Inflammatory Bowel Disease

Professor Jean-Frédéric Colombel

The three pillars of optimal care in IBD are early intervention, T2T, and TC,[14] all of which are built on a foundation of communication with the patient and hence, require patient empowerment.

A T2T approach involves predefining a treatment target in consultation with the patient, continuously monitoring disease activity, and modifying treatment until the target is reached. The aim is not only to control symptoms, but also to block disease progression in order to avoid bowel damages and disability. In 2015, it was proposed in the STRIDE guidelines[8] that the target in CD should be a composite endpoint of clinical and endoscopic remission, with clinical remission defined as resolution of abdominal pain and normalisation of bowel habit that should be assessed every 3 months during active disease. Patients' individual goals and specific challenges, such as perianal disease, should also be taken into account. Endoscopic remission was defined as resolution of ulceration, assessed by endoscopy 6–9 months after initiation of therapy. When the disease is mainly located in the small bowel, cross-sectional imaging should be used. In 2015, biomarkers such as C-reactive

protein (CRP) and faecal calprotectin were not considered targets but, rather, adjunctive measures of inflammation used to achieve TC. Histologic remission was not considered a target in 2015.

In UC, the same concept of a composite target was proposed.[8] Clinical remission was defined as resolution of rectal bleeding and normalisation of bowel habit, assessed every 3 months during active disease. Patients' individual goals including mood disorders, fatigue, and work productivity should be included in the target. Endoscopic remission was defined as the resolution of friability and ulceration, assessed via flexible sigmoidoscopy or colonoscopy (Mayo score 0–1) within 3–6 months of initiation of therapy. Again, biomarkers such as CRP and faecal calprotectin are adjunctive measures of inflammation, not targets, for monitoring UC and histologic remission was not considered a target in 2015 due to lack of evidence of its clinical utility; however, Prof Colombel noted this might evolve.

The final pillar is TC. In order to reach the target, the patients' symptoms and biomarkers need to be monitored regularly. The two main biomarkers used currently as part of this approach are CRP and faecal calprotectin. The CALM study[1] was an open-label, multicentre, Phase III study in Europe and Canada, designed to compare two treatment algorithms: a conventional management approach and TC treatment algorithm in newly diagnosed CD patients. Patients (n=244) received up to 8 weeks prednisolone before randomisation to conventional management or TC. In the conventional management arm, treatment escalation was based on symptoms or steroid use; in the TC arm, treatment escalation was based not only on symptoms or steroid use but also on CRP or faecal calprotectin levels. Assessments took place every 12 weeks. In the TC arm, if a patient was in clinical remission but biomarker levels were raised, treatment was escalated. The escalation sequence was no treatment, adalimumab EOW, adalimumab weekly, and finally adalimumab weekly plus azathioprine. There was an option for rescue if treatment escalation was needed before the next assessment. Treatment could also be de-escalated.

The results from the CALM study show that a higher proportion of patients in the TC arm achieved the primary endpoint of mucosal healing (CDEIS <4) and no deep ulcerations at Week 48 (56/122; 46%) compared with the clinical management group (37/122; 30%). At the end of the study, all secondary endpoints were achieved by more patients in the TC than in the conventional management arm. Deep remission, for example, a composite for clinical and endoscopic remission, was achieved by 36.9% of those in the TC arm compared with 23.0% in the conventional management arm (p=0.014).[1] The CALM study concluded that timely escalation with an anti-TNF therapy on the basis of clinical symptoms combined with biomarkers in patients with early CD resulted in better clinical and endoscopic outcomes than symptom-driven decisions alone.

Escalation of therapy based on biomarker levels meant that, overall, patients in the TC arm received earlier and more intensive treatment. Prior to randomisation, the reasons for escalation were similarly represented and included symptoms (CDAI, prednisone use), as well as biomarker levels (CRP and faecal calprotectin). As the study progressed, escalation became primarily driven by biomarker levels.

De-escalation of treatment once targets are reached remains a topic of interest, but Prof Colombel urged caution when considering de-escalation because of the lack of evidence to support it. Further analysis of the CALM data[15] found that, in the small numbers of patients who de-escalated treatment, 61% of those in TC arm (n=23) and 54% in the clinical management arm (n=13) achieved mucosal healing at Week 48. In the TC arm, 75% (n=8) of patients who de-escalated treatment and then required re-escalation achieved mucosal healing at Week 48.

A key finding in follow-up of the CALM data was that, 1 year after randomisation, there were significantly fewer CD-related hospitalisations in the TC group (13.2 events/100 patient-years; n=122) compared with the clinical management group (n=122; 28.0 events/100 patient-years; n=122; p=0.021).[16] A 5-year follow-up of CALM hospitalisation data is expected soon.

Prof Colombel stressed that the concept of TC and monitoring is simple to implement in practice (see Figure 2). Patients are stratified according to their symptoms and objective data, especially

from endoscopy. Treatment is initiated and, at 3 months, CRP and calprotectin levels are monitored. At 6–9 months, colonoscopy is performed and if the target (no symptoms, no positive surrogate marker, and no mucosal ulceration) has been achieved, treatment is continued. If not, the treatment is optimised or changed.

In conclusion, T2T and TC are complementary approaches that should be tailored to the individual patient. The STRIDE guidelines[8] for endoscopic mucosal healing are based on a post hoc analysis and there is currently no prospective study demonstrating that treating to endoscopy is more effective than to symptoms. However, the prospective REACT2 trial[17] is ongoing.

Breaking Down Barriers: A Patient Case of Treat to Target

Professor Remo Panaccione

To illustrate how to apply the discussed strategies in clinical practice, Prof Panaccione presented two cases: Case 1 from 2013 and Case 2 from 2018. Both were 22 years old at the time of admission with similar symptoms, including weight loss, abdominal pain, and diarrhoea. Case 1 took 3 years to seek help; Case 2 took 3 months. Consequently, at diagnosis, Case 1 had anaemia, was iron-deficient, and was malnourished; Case 2 was not. Case 1 had to wait 6 months to be referred to a gastroenterologist; Case 2 benefitted from an expedited referral and was seen in 4 weeks. At the initial consultations, examination revealed that both women had a 20 cm deep ulceration in the terminal ileum, 30 cm ileal inflammation, and mild narrowing. Case 2 also had biomarker assessment indicating normal CRP but a faecal calprotectin level of 800 µg/g. In both women, prednisolone was initiated and both experienced symptom improvement at 3-month follow-up. Case 1 underwent no additional monitoring, but Case 2's biomarkers were assessed again: calprotectin was 450 µg/g, lower than at diagnosis, but too high to be indicative of controlled inflammation. Based on discussion with her physician, despite feeling better, Case 2 initiated treatment with adalimumab (induction dose 160/80 mg; 40 mg EOW).

At 6 months, Case 1 had recurrent symptoms and started on prednisone and azathioprine.

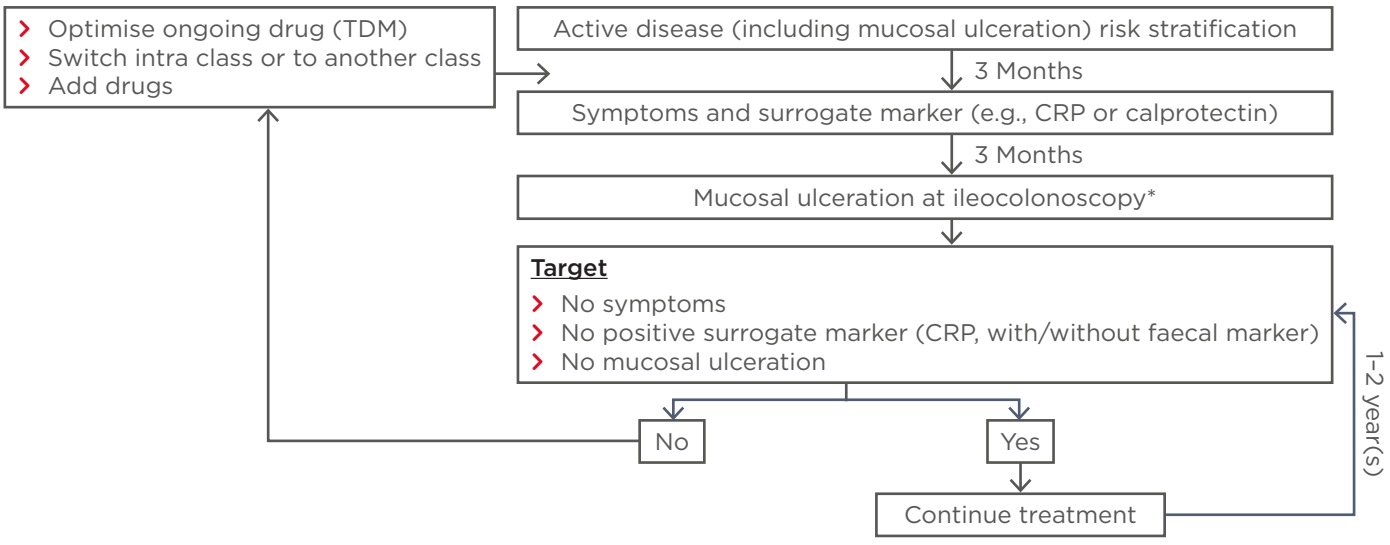


Figure 2: Implementation of treat to target with tight control and monitoring in practice.

*Or resolution of findings of inflammation on cross-sectional imaging in patients who cannot be adequately assessed with ileocolonoscopy.

CRP: C-reactive protein; TDM: therapeutic drug monitoring.

Adapted from Bouguen et al. [9]

Case 2 was asymptomatic, but the calprotectin level remained elevated (390 µg/g) and consequently her adalimumab dose was increased to 80 mg EOW. She remained asymptomatic on this dose thereafter, with fully controlled disease.

At 9 months, Case 1 was admitted to hospital with pain, bloating, and vomiting; she received intravenous corticosteroids, an induction dose of adalimumab, and continued treatment with 40 mg EOW. She continued to have intermittent symptoms, switched to infliximab therapy with no improvement, and underwent a 40 cm ileocaecal resection with primary anastomosis.

Prof Panaccione commented that the management seen in Case 1 is common in practice: delayed diagnosis, a lack of monitoring and no optimisation of treatment, and biologic treatment initiated too late. Disease progression and advanced structural damage were the consequences in Case 1's case. By contrast, the strategy of T2T and TC used in Case 2, with decisions based on discussion, education, and monitoring, resulted in full disease control. It was noted that physicians must respect the values of patients and their views on the therapeutic journey regarding monitoring and optimising treatment. However, research from CALM,[1] among other studies, suggests that the management of IBD will evolve significantly, not because of different therapeutic agents, but due to different implementation strategies.

Looking Beyond Inflammatory Bowel Disease: Effecting Change in Patients' Lives

Professor Edouard Louis

IBD has an impact on patients' lives, not only during periods of active disease, but also between flares. The IMPACT study,[18] conducted by the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA) included 4,670 patients with IBD. The study found that, even between flares, almost half (49% of CD patients; 47% of UC patients) responded that their life was somewhat or significantly affected by the disease during the course of everyday activities.

The IMPACT study[18] also found that the majority of patients would like better communication with their gastroenterologist. Most (64%) felt that the gastroenterologist should ask more probing questions (sometimes or more frequently), while 31% of respondents were satisfied with their consultations. Similarly, 54% of patients reported that they had no opportunity to tell their gastroenterologist something potentially important (sometimes or more frequently) compared with 41% who were satisfied.

Prof Louis felt this finding may explain the discrepancy between physician and patient assessment of disease, with physicians reporting full control of disease more frequently than their patients. For instance, a web-based questionnaire, completed by adult UC patients and their physician in Europe and Canada, found that 43% of physicians (n=475) believed their patients' symptoms to be completely or mostly under control. By contrast, only 26% of patients (n=775) reported this to be the case.[19]

As a result of such findings, both the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) have implemented new criteria for drug development in IBD[20,21] that include both mucosal healing and validated PRO. The EMA guidance states that coprimary endpoints in UC are endoscopic Mayo score of 0–1 and no reports of PRO, including bleeding. Likewise, in CD, mucosal healing is assessed by a score (e.g., Crohn's Disease Endoscopic Index of Severity [CDEIS]=0) and the PRO include number of stools and abdominal pain.

Increased efforts are being made to report PRO. The PYRAMID registry[22] includes patients with CD treated with adalimumab and followed for up to 6 years. Scores from the health-related Short IBD questionnaire completed by these patients suggest a clinically meaningful improvement of ≥9 points from baseline at 1 year and maintained over 6 years. The work productivity and activity impairment index (WPAI) is used to assess four domains: absenteeism, presenteeism (under-performance at work), overall work impairment, and activity impairment. Patients included in the PYRAMID registry[22] reported clinically meaningful improvements in WPAI across all domains at almost all time points (defined as an improvement of ≥7 points from baseline at <2 years, 2–<5 years, 5–<10 years, and ≥10 years).

Disease duration prior to initiation of treatment was shown to be important. Numerically greater improvements in overall work impairment, for example, were seen in patients with CD duration <5 years compared to ≥5 years. The impact of adalimumab is clinically meaningful in both groups but is less pronounced when treatment is introduced later in the course of disease. Prof Louis said there is disease progression at both the tissue and the psychosocial level.

A variety of PRO have been used in clinical trials, but, according to Prof Louis, many have been developed without the participation of patients.[23] Therefore, they do not always tackle the questions that are most relevant to the patient. He advocated the use of communication tools such as the IBD Disk, which was based on the validated disability index.[11] Patient focus groups selected relevant issues that were then agreed upon by an expert consensus group.[24] The IBD Disk includes 10 items: abdominal pain, regulating defecation, interpersonal interactions, education and work, sleep, energy, emotions, body image, sexual functions, and joint pain. Patients score each item (0–10) on a coloured disc, which results in a highly visual tool for assessing IBD-associated disability. Frequent use of the tool allows the impact of the disability to be followed over time, disease management goals to be set for the short and long term, and treatment efficacy to be monitored. It may also encourage adherence to medication by demonstrating to patients that the treatment is impacting issues that are important to them personally. This tool provides a comprehensive assessment of quality of life and alongside this also highlights specific problems and may therefore facilitate discussions between the patient and the physician that might not have occurred without its use. Physicians using the IBD Disk or other tools must be prepared to address issues raised as a result of this assessment. A collective approach involving other professionals, such as psychologists, dieticians, social workers, and nurses, can assist patients in coping with their disease in daily life.

In conclusion, Prof Louis stressed the importance of discussions with patients on the burden of disease beyond their clinical symptoms, including quality of life, daily living, and work productivity. The IBD Disk is a good example of a tool developed in partnership with patients that highlights broad and/or specific disease-related issues that impact patients' daily life.

Panel Discussion Points

- The STRIDE guidelines[8] include a target of complete mucosal healing. Indirect evidence suggests that a target of histological healing may improve outcomes further, but there is insufficient evidence to implement this in clinical practice today. Treating to more stringent targets will lead to more failure of therapy and potentially lower adherence.
- The suggested threshold at which treatment is escalated is changing frequently as new evidence becomes available, but regular monitoring is undisputed. Monitoring and treatment optimisation may be cost-effective if savings from decreased hospitalisation, physician consultations, and work productivity are taken into account.
- Physicians are urged to not undertreat, especially in cases of proctitis. They may be reluctant to initiate biologic therapy for 5–10 cm of disease activity, but loss of rectal function leads to distressing symptoms such as faecal urgency and incontinence. Early control of inflammation in UC is essential to maintain function.
- Disease progression assessment should include psychosocial damage and motivate physicians to initiate treatment early in disease. Loss of professional and/or social life may be irreversible and may be as important to patients as tissue damage.
- TC is feasible in clinical practice when patients are motivated; non-adherence may occur if they do not understand the rationale. Targets which integrate quality of life factors may increase patients' motivation.
- There is currently a lack of evidence on dose de-escalation but the topic should be discussed with patients in order to decrease the possibility of patients stopping treatment without medical supervision.

Conclusion

Prof Panaccione closed the symposium by stressing that both CD and UC are progressive

diseases. Early intervention and personalised risk stratification are part of a T2T strategy in which the target is a composite endpoint of clinical and endoscopic remission, agreed in discussion with the patient. The CALM study demonstrated that timely escalation with an anti-TNF therapy on the basis of clinical symptoms combined with biomarkers in patients with early CD resulted in better clinical and endoscopic outcomes than symptom-driven decisions alone.

A T2T strategy involves TC and prevention of disease progression. Regular disease monitoring through visits, biomarker assessment, and timely endoscopy is essential. Current evidence suggests that this approach can change the course of IBD, but more data are needed to confirm the long-term benefits.

Additionally, patient factors beyond clinical symptoms must be considered. PRO tools and communication strategies can enhance patient engagement in shared decision-making and help physicians support patients in achieving both clinical goals and those involved in succeeding in their daily life.

Prof Panaccione noted he believes that the course of IBD can be changed and commented that early intervention, T2T, and TC are the pillars for supporting change, all of which are based on a foundation of good and open communication with the patient.

References

1. Colombel JF et al. Effect of tight control management on Crohn's disease (CALM): A multicentre, randomised, controlled Phase 3 trial. Lancet. 2017;390(10114):2779-89.
2. Crohn B et al. Regional ileitis: A pathologic and clinical entity. JAMA. 1932;99(16):1323-9.
3. Thia KT et al. Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. Gastroenterology. 2010;139(4): 1147-55.
4. Fiorino G et al. Prevalence of bowel damage assessed by cross-sectional imaging in early Crohn's disease and its impact on disease outcome. J Crohns Colitis. 2017;11(3):274-80.
5. Pariente B et al. Development of the Crohn's disease digestive damage score, the Lémann score. Inflamm Bowel Dis. 2011;17(6):1415-22.
6. Panaccione R et al. Adalimumab efficacy and safety by disease duration: Analysis of pooled studies of Crohn's disease. Gastroenterology. 2017;152(5 Suppl 1):S744.
7. Colombel JF et al. Adalimumab induces deep remission in patients with Crohn's disease. Clin Gastroenterol Hepatol. 2014;12(3): 414-22.e5.
8. Peyrin-Biroulet L et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): Determining therapeutic goals for treat-to-target. Am J Gastroenterol. 2015;110(9): 1324-38.
9. Bouguen G et al. Treat to target: A proposed new paradigm for the management of Crohn's disease. Clin Gastroenterol Hepatol. 2015;13(6):1042-50.e2.
10. Peyrin-Biroulet L et al. Systematic review: Outcomes and post-operative complications following colectomy for ulcerative colitis. Aliment Pharmacol Ther. 2016;44(8):807-16.
11. Gower-Rousseau C et al.; International programme to develop new indexes for Crohn's Disease (IPNIC) group. Validation of the Inflammatory Bowel Disease Disability Index in a population-based cohort. Gut. 2017;66(4):588-96.
12. Torres J et al. Ulcerative colitis as a progressive disease: The forgotten evidence. Inflamm Bowel Dis. 2012;18(7):1356-63.
13. Fumery M et al. Detection of dysplasia or cancer in 3.5% of patients with inflammatory bowel disease and colonic strictures. Clin Gastroenterol Hepatol. 2015;13(10):1770-5.
14. Colombel JF et al. Management strategies to improve outcomes of patients with inflammatory bowel diseases. Gastroenterology. 2017;152(2):351-61.e5.
15. Bossuyt P et al. De-esclating therapy in patients with Crohn's disease receiving adalimumab: A subgroup analysis of the CALM study. Abstract P1614. UEG Week, 20-24 October, 2018.
16. Colombel JF et al. A treat to target approach decreases the rate of CD-related adverse outcomes versus a clinical approach in patients with moderate to severely active Crohn's disease: data from CALM. Abstract 1057. UEG Week, 28 October-1 November, 2017.
17. University of Western Ontario, Canada. Enhanced algorithm for Crohn's treatment incorporating early combination therapy (REACT2). NCT01698307. https://clinicaltrials.gov/ct2/show/NCT01698307.
18. Lönnfors S et al. IBD and health-related quality of life - Discovering the true impact. J Crohn's Colitis. 2014;8(10):1281-6.
19. Schreiber S et al. Perception gaps between patients with ulcerative colitis and healthcare professionals: An online survey. BMC Gastroenterol. 2012;12(1):108.
20. European Medicines Agency. Guidelines on the development of new medicine products for the treatment of Crohn's disease. 2016. Available at: https://www.ema.europa.eu/documents/scientific-guideline/draft-guideline-development-new-medicinal-products-treatment-crohns-disease-revision-2_en.pdf. Last accessed: 19 November 2018.
21. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Ulcerative colitis: Clinial trial end-points. Guidance for industry. 2016. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM515143.pdf. Last accessed: 19 November 2018.
22. Loftus EV Jr et al. Long-term effectivemess and safety of adalimumab based on Crohn's disease duration: Results from the PYRAMID registry. J Crohns Colitis. 2018;12(Suppl 1):S493-4.
23. de Jong MJ et al. Patient-reported outcome measures for use in clinical trials and clinical practice in inflammatory bowel diseases: A systematic review. Clin Gastroenterol Hepatol. 2018;16(5):648-63.e3.
24. Ghosh S et al. Development of the IBD Disk: A visual self-administered tool for assessing disability in inflammatory bowel diseases. Inflamm Bowel Dis. 2017;23(3): 333-40.

Abstract Reviews

Discover the latest research and results as *EMJ Gastroenterology* brings to you abstract reviews of presentations made at UEG Week 2018

Effects of Dietary Fibres on Indomethacin-Induced Intestinal Permeability in Elderly People: A Randomised Placebo Controlled Parallel Clinical Trial

Authors: John-Peter Ganda Mall,[1] Frida Fart,[1] Julia Sabet,[1] Carl-Mårten Lindqvist,[1] Åsa Keita,[2] Robert-Jan Brummer,[1] *Ida Schoultz[1]

1. Department of Medical Sciences, Örebro University, Örebro, Sweden
2. Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden

*Correspondence to ida.schoultz@oru.se

Disclosure: This study was financed by the European Commission's seventh framework programme FibeBiotics. Bioactor (Netherlands) and Swedish Oat Fiber (Sweden) provided the study supplement arabinoxylan and oat β-glucan, respectively, but had no involvement in the design, analysis, or interpretation of the results in this study.

Acknowledgements: Many thanks to the United European Gastroenterology (UEG) Week and the European Medical Journal for wishing to publish this abstract review. We would also like to acknowledge the FibeBiotics EU consortium and collaboration performed within this organisation, particularly Dr Ellen Kranenbarg-Stolte at Wageningen University, Wageningen, Netherlands, for her excellent work measuring the cytokines in this study. We would also like to thank Nordic Sugar (Sweden), Solactis (France), Biogaia (Sweden), Univar (Sweden), and Ingredi (Sweden) for providing us with the separate sugar probes needed for the *in vivo* multisugar permeability test. Finally, we would like to thank all study participants for taking part in this study.

Keywords: Clinical trial, dietary fibre, elderly, gut health, inflammation, intestinal barrier function, non-steroid anti-inflammatory drugs, oral supplementation, prebiotics, permeability.

Citation: EMJ Gastroenterol. 2018;7[1]:68-70. Abstract Review No. AR1.

INTRODUCTION

The global population of elderly (>65 years) people is increasing and will have a major impact on healthcare systems[1,2] due to an increase in age-related diseases. Gastrointestinal (GI) symptoms are common among the elderly and the elevated pharmaceutical load in elderly

patients is of potential harm to the intestine. It is known that long-term use of non-steroid anti-inflammatory drugs, commonly used for pain management among the elderly, can cause gastric ulceration, enteropathy,[3,4] and increased intestinal permeability.[5] A deteriorated barrier function is associated with increased psychological distress in the elderly with GI symptoms,[6] and we have previously shown that specific dietary fibres can attenuate stress-induced hyperpermeability *ex vivo* in elderly patients with GI symptoms[7] and patients with Crohn's disease.[8] However, the potential of dietary fibres to strengthen the intestinal barrier function *in vivo* in elderly individuals is, to our knowledge, not known.

AIM

We performed a randomised, double-blind, placebo-controlled parallel clinical trial to investigate whether 6 weeks of oral supplementation of wheat-derived arabinoxylan or oat β-glucan could strengthen the gut barrier function in elderly individuals and reduce indomethacin (a non-steroidal anti-inflammatory drug)-induced gut permeability. Furthermore, changes in gut microbiota composition, inflammatory/oxidative status, and self-reported health were evaluated after intervention.

METHODS

All qualified subjects (n=49) participated in a three-arm study design. Each arm consisted of 6 weeks of intervention with arabinoxylan, oat β-glucan, or placebo (maltodextrin). The primary outcome was set to changes in indomethacin-induced intestinal permeability before and after intervention as assessed by an *in vivo* multisugar test. Secondary outcomes were set to changes in microbiota composition, systemic inflammatory/oxidative status, and self-reported health. Blood and faecal samples were collected at both the beginning and end of the study. Dietary intake was estimated using a food frequency questionnaire.

RESULTS

Indomethacin was found to significantly increase small intestinal permeability in all three intervention arms, while colonic permeability was significantly increased in only one of the intervention arms. No significant effects on the primary parameters (intestinal permeability) or secondary parameters (microbiota, inflammatory/oxidative levels and self-reported health) were observed after intervention with either dietary fibre compared to placebo. Food frequency questionnaire analysis revealed that 85% of all elderly participants had an insufficient fibre intake, accounting only for a median of 64.6% (IQR 50.6–83.8%) of the Nordic Nutrition Recommendations.

CONCLUSION

Our data show that supplementation of arabinoxylan or oat β-glucan was not able to attenuate indomethacin-induced intestinal permeability. However, our results show that dietary fibre intake among the elderly was below the Nordic Nutrition Recommendations levels. This emphasises the importance to further investigate the effect of dietary fibres on gut health and barrier function in elderly for the development of appropriate dietary guidelines regarding supplementation of dietary fibres.

DISCUSSION AFTER PRESENTATION

Many relevant questions were raised and discussed after the presentation. Particularly, questions regarding how the oral supplements were delivered and ingested and concerns about the impact of the food matrix that the supplements were mixed with were addressed. The supplements were delivered in powder form and were either sprinkled over breakfast or taken in a morning drink. This led to further discussion about the compliance of the study participants, which was verified by counting the remaining study products returned after the study. The discussion was very meaningful and contributed to the possible explanations of the results and their implications, which will be very useful when finalising the authors' research manuscript.

References

1. Cohen JE. Human population: The next half century. Science. 2003;302(5648):1172-5.
2. Dennison C et al. The health-related quality of life and economic burden of constipation. Pharmacoeconomics. 2005;23(5):461-76.
3. Lagerin A et al. Extent and quality of drug use in community-dwelling people aged ≥75 years: A Swedish nationwide register-based study. Scand J Public Health. 2017. [Epub ahead of print].
4. Bjarnason I et al. Effect of non-steroidal anti-inflammatory drugs and prostaglandins on the permeability of the human small intestine. Gut. 1986;27(11):1292-7.
5. van Wijck K et al. Novel multi-sugar assay for site-specific gastrointestinal permeability analysis: A randomized controlled crossover trial. Clin Nutr. 2013;32(2):245-51.
6. Ganda Mall JP et al. Are self-reported gastrointestinal symptoms among older adults associated with increased intestinal permeability and psychological distress? BMC Geriatr. 2018;18(1):75.
7. Ganda Mall JP et al. Differential effects of dietary fibres on colonic barrier function in elderly individuals with gastrointestinal symptoms. Sci Rep. 2018;8(1):13404.
8. Ganda Mall JP et al. A β-glucan-based dietary fiber reduces mast cell-induced hyperpermeability in ileum from patients with crohn's disease and control subjects. Inflamm Bowel Dis. 2017;24(1):166-78.

Patient-Derived Organoid-Based Prediction of Concurrent Chemoradiotherapy Response in Oesophageal Cancer

Authors: *Su Youn Nam, Seung Jin Lee, Seong Woo Jeon

Kyungpook National University Hospital, Daegu, South Korea
*Correspondence to nam20131114@gmail.com

Disclosure: This project was funded by the National Research Foundation, South Korea (NRF-2015R1D1A1A01059219).

Keywords: Concurrent chemoradiotherapy (CCRT), oesophageal cancer, patient-derived primary organoid, precision medicine.

Citation: EMJ Gastroenterol. 2018;7[1]:70-72. Abstract Review No. AR2.

BACKGROUND

Oesophageal carcinoma is the eighth most common malignancy worldwide and the seventh most common cause of death in men.[1] Most patients are diagnosed with oesophageal cancer in the advanced stages, with approximately 20% of cases being resectable.[1] Concurrent chemoradiotherapy (CCRT) is superior to radiotherapy alone for patients with locally advanced oesophageal cancer.[2] Definitive CCRT is a well-established treatment for oesophageal cancer, but many patients do not achieve remission with CCRT alone. Although several clinical and molecular markers can be used to evaluate the response to CCRT, they are not highly predictive. Ridky et al.[3] found that the correlation between the primary tumour and a two-dimensional cell culture was very low, whereas the similarity between a three-dimensional tissue environment and the primary tumour was higher than the mouse to human correlation.[3] Patient-derived organoids have advantages in providing more physiologically relevant and predictive data for *in vivo* responses.

AIM

Our aim was to evaluate the predictive power of CCRT response using a primary three-dimensional cell (organoid) culture in oesophageal cancer.

METHODS

Patient-derived organoid culture was performed using tumour tissues acquired from patients with oesophageal cancer before they began treatment with CCRT. After culturing the tissues for 7 days, same-sized organoids were collected and treated with fluorouracil (5-FU) and 5Gy radiotherapy. After 6 days, the primary cultured cells were stained and fluorescent images were

captured. The clinical response was assessed after the fourth cycle of CCRT. Clinical response was classified as complete remission (CR), partial remission (PR), or disease progression (PD).

RESULTS

A total of 27 oesophageal cancer patients were enrolled. The final success rate of the patient-derived organoid culture was 78% (21/27). The CCRT response in patient-derived organoids was evaluated in 21 cases. A total of 16 people were followed-up for >4 cycles of CCRT and were analysed. Clinical CR was observed in 10 patients and 6 showed clinical PR (n=4) or PD (n=2). Strong live activity (green fluorescent image) was noted in the control group, whereas extremely low live activity and strong dead activity (red fluorescent image) was observed in the CCRT group (Figure 1A). In the clinical setting, these patients achieved long-term CR. Strong live activity was noted in the control group and also in the CCRT group (Figure 1B). In the clinical setting, these patients showed initial PD. Live activity was noted in <10% of organoids in all patients with clinical CR and was observed in 30–40% of organoids in all patients with clinical PD. Live activity was noted in <20–30% of organoids in all patients with clinical PR. Among 16 patients, organoid-based CCRT response prediction was matched with clinical CCRT response in 15 patients (93%) and 1 case was unmatched.

DISCUSSION

It took 2 weeks to evaluate the CCRT response in organoids from tissue acquirement. Furthermore, a high agreement between clinical response and response in organoids was observed. Therefore, the evaluation of CCRT response using patient-derived primary organoids will provide a good predictor of clinical CCRT response, making precision medicine one step closer. Investigation for the molecular similarity between primary tissue and patient-derived organoids will provide more concrete evidence for the usefulness of patient-derived organoids.

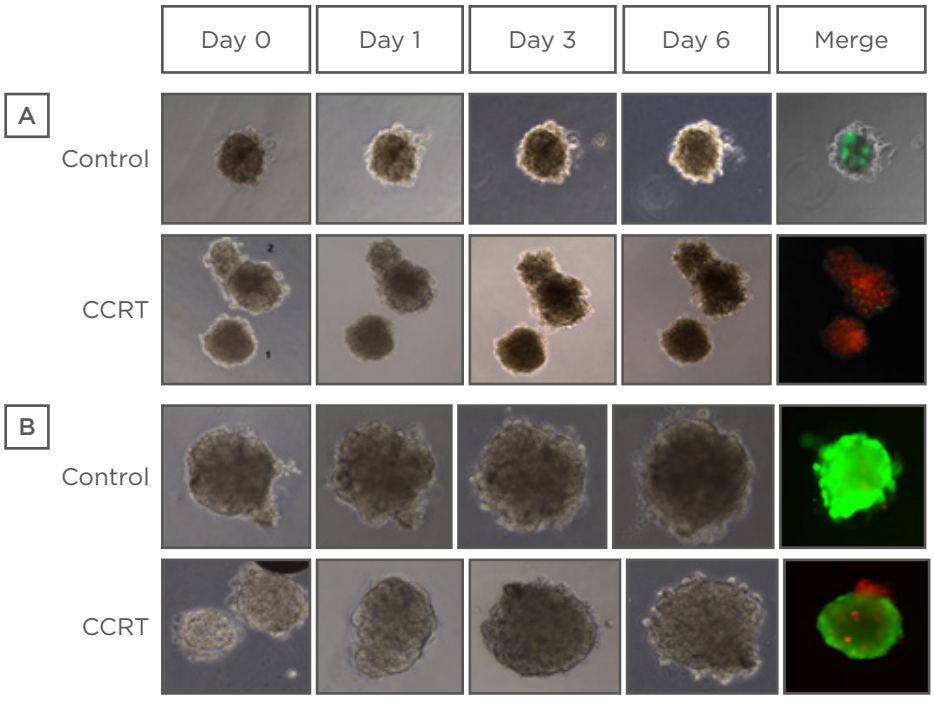


Figure 1: Concurrent chemoradiotherapy response in patient-derived primary organoids.

A) Strong live activity (green fluorescent image) was noted in the control group, whereas extremely low live activity and strong dead activity (red fluorescent image) were observed in the CCRT group. B) Strong live activity was noted in the control group and also in the CCRT group.

CCRT: concurrent chemoradiotherapy.

References

1. Siegel RL et al. Cancer statistics, 2016. CA Cancer J Clin. 2016;66(1):7-30.
2. al-Sarraf M et al. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: An intergroup study. J Clin Oncol. 1997;15(1):277-84.
3. Ridky TW et al. Invasive three-dimensional organotypic neoplasia from multiple normal human epithelia. Nat Med. 2010;16(12):1450-5.

Predictive Value of PAGE-B Score in Tunisian Patients with Chronic Hepatitis B Treated with Entecavir

Authors: *Nawel Bellil, Rym Ennaifer, Bochra Bouchabou

Department of Gastroenterology, Mongi Slim Hospital, LaMarsa, Tunisia
*Correspondence to bellilnawara@gmail.com

Disclosure: The authors have declared no conflicts of interest.

Keywords: Chronic hepatitis B virus (HBV), cirrhosis, entecavir, hepatocellular carcinoma, PAGE-B, risk prediction models.

Citation: EMJ Gastroenterol. 2018;7[1]:72-74. Abstract Review No. AR3.

INTRODUCTION AND AIMS

Current first-line oral nucleos(t)ide analogues, entecavir (ETV) and tenofovir, have had a major impact on chronic hepatitis B virus (HBV) (CHB) treatment. Nevertheless, the risk of developing hepatocellular carcinoma (HCC) cannot be completely eliminated regardless of long-term virological remission,[1] thus, risk stratification and early detection of HCC are of great importance for patients with CHB. Several scores for predicting the risk of HCC have been developed.[2] Recently, a risk score was developed for Caucasians receiving ETV or tenofovir called the PAGE-B score. This score estimates HCC risk within the first 5 years of treatment.[3]

Our study aimed to identify predictors of HCC in Tunisian CHB patients treated with ETV, to assess predictive performance of the PAGE-B risk score, and to compare its accuracy with other HCC risk prediction models, such as the REACH-B score, before and during treatment.

PATIENTS AND METHODS

This is a retrospective study covering 5 years (2011–2016) and including all patients with CHB with or without cirrhosis undergoing ETV for at least 12 months. The date of enrolment was the first day of treatment. Excluded patients were those with hepatitis C virus (HCV), HIV, or hepatitis D virus (HDV) coinfection; co-existing primary liver disease; HCC at enrolment; and HCC development within 12 months after enrolment. Clinical and biological examinations and abdominal ultrasound were performed every 6 months. Diagnosis of HCC was based on findings from sectional imagery or on histological evidence.[4] PAGE-B and REACH-B scores were calculated at enrolment and 1 year after treatment. The PAGE-B score is based on age, sex, and platelet count at the start of therapy.[3] The REACH-B model includes age, sex, alanine aminotransferase level, hepatitis B e antigen (HbeAg) status, and HBV DNA level as variables.[5] Predefined thresholds (10 and 17 for PAGE-B and 8 for REACH-B) allowed us to classify patients according to the probability of developing HCC.

RESULTS

Overall, 67 patients were enrolled with a mean age of 47 years (24–73 years). Twenty-eight patients (43%) had been previously treated with pegylated IFN in 25 cases and lamivudine in 3 cases. Thirty-six patients (55%) had cirrhosis.

Table 1: Independent predictors of hepatocellular carcinoma development.

Baseline clinical characteristics	Value	Univariate p value	Multivariate p value	Hazard ratio (95% CI)
Age (years)	47±9	0.018	0.030	2.762 (1.324–12.552)
Male sex	52 (77.0%)	0.042	0.280	NA
Diabetes	10 (14.9%)	0.136	NA	NA
Cirrhosis	36 (53.7%)	<0.010	0.150	NA
Treatment experienced	28 (41.0%)	0.600	0.330	NA
Laboratory variables				
HBeAg positivity	6 (8.9%)	0.058	0.046	3.567 (1.435–9.542)
HBV DNA (Log UI/mL)	4.5±0.5	0.021	0.120	NA
Platelet count (10^9/L)	220±44	<0.010	0.012	0.541 (0.132–0.633)
Alanine aminotransferase (IU/L)	61±10	0.430	NA	NA
Total bilirubin (µmol/L)	26±7	0.013	0.430	NA
Serum albumin (g/L)	36.0±0.5	0.069	0.320	NA

CI: confidence interval; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; NA: not applicable.

Six patients (9%) were HbeAg-positive. HCC occurred in 14 patients (20%) within 5 years, with a mean duration of 45 months (12–58 years). Thirteen (92%) of these patients were cirrhotic. At 1 year of ETV, virological remission was obtained in 51 patients (75%), increasing to 90% at 2 years without reducing the risk of HCC (p=0.53). Univariate and subsequent multivariate Cox proportional hazard regression analyses showed that older age, male sex, and HBeAg positivity were independent predictors of HCC development (Table 1). The area under the receiver operating characteristic curve of PAGE-B was significantly higher than that of the REACH-B (0.91 versus 0.80 at 5 years, p=0.03). When calculated at 1 year after ETV, the PAGE-B showed higher predictability than that of the REACH-B, with an area under the receiver operating characteristic curve value of 0.88 versus 0.67 and 95% confidence interval of 0.769–0.992 and 0.566–0.972, respectively, p=0.001. Five-year HCC-free survival in patients with a PAGE-B score ≤10 was 94% versus 62% with a PAGE-B score >10 and 30% with a PAGE-B score ≥17 (p<0.010). Furthermore, the 5-year HCC-free survival in patients without cirrhosis with a PAGE-B score <10 was 100%.

DISCUSSION AND CONCLUSION

Our study confirmed that the risk of HCC persists in CHB patients treated with ETV regardless of virological remission. Older age, lower platelet count, and positive HbeAg were independent predictors of HCC occurrence. These factors have been widely described in the literature as being predictive of HCC development: age reflects accumulation of liver damage;[6] platelet count represents a marker of liver disease severity and may be a more reliable factor than cirrhosis itself;[7] and HbeAg positivity is associated with a recurrence of cycles of necrosis and regeneration, which increases the probability of malignant transformation. Moreover, our study showed that PAGE-B had high accuracy for the prediction of HCC development in this sample of CHB Tunisian patients treated with ETV. This score is, therefore, reliable, easy to calculate, reproducible, and dynamic. In addition, we identified a particular group of patients (CHB without cirrhosis with a PAGE-B score <10) who had an almost zero risk of developing HCC within 5 years of treatment and, therefore, do not require close supervision.

References

1. Papatheodoridis GV et al. Risk of hepatocellular carcinoma in chronic hepatitis B: Assessment and modification with

current antiviral therapy. J Hepatol. 2015;62(4):956-67.
2. Lee HW, Ahn SH. Prediction models of hepatocellular carcinoma development in chronic hepatitis B patients. World J Gastroenterol. 2016;22(37):8314-21.
3. Papatheodoridis G et al. PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. J Hepatol. 2016;64(4):800-6.
4. Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology. 2005;42(5):1208-36.
5. Yang H-I et al. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): Development and validation of a predictive score. Lancet Oncol. 2011;12(6):568-74.
6. Hsu Y-C et al. Determinants of hepatocellular carcinoma in cirrhotic patients treated with nucleos(t)ide analogues for chronic hepatitis B. J Antimicrob Chemother. 2014;69(7):1920-7.
7. Papatheodoridis GV et al. The risk of hepatocellular carcinoma decreases after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B. Hepatology. 2017;66(5):1444-53.

Diagnostic and Prognostic Values of Both S100 Calcium Binding Protein A4 (S100A4) and Glypican 3 in the Tissues of Hepatocellular Carcinoma in Egyptian Cirrhotic Hepatitis Virus C Patients: A Tissue Microarray-Based Study

Authors: *Mahmoud El-Bendary,[1] Khaled Farid,[1] Ahmed El-Mesery,[1] Mohammad Arafa,[2] Wagdi Elkashef,[2] Talaat Abdullah[3]

1. Tropical Medicine and Hepatology Department, Mansoura Faculty of Medicine, Mansoura University, Mansoura City, Egypt
2. Pathology Department, Mansoura Faculty of Medicine, Mansoura University, Mansoura, Egypt
3. Gastroenterology Surgery Center, Mansoura Faculty of Medicine, Mansoura University, Mansoura, Egypt

*Correspondence to mmelbendary@gmail.com

Disclosure: The authors have declared no conflicts of interest.

Keywords: Glypican-3 (GPC3), hepatocellular carcinoma (HCC), S100 calcium binding protein A4, tissue microarray.

Citation: EMJ Gastroenterol. 2018;7[1]:74-75. Abstract Review No. AR4.

The S100 protein family is a multigenic group of non-ubiquitous, cytoplasmic, EF-hand, Ca^{2+}-binding proteins, sharing significant structural similarities at both genomic and proteomic levels.[1] The S100 proteins have been reported to be implicated in the inflammatory response process, as well as in the metastatic development of several cancers.[2] S100 calcium binding protein A4 (S100A4), which is related to epithelial mesenchymal transition (EMT), is mainly involved in metastasis. Hepatocellular carcinoma (HCC) cell S100A4 expression, together with other EMT-related proteins, is indicative of metastasis and informs overall survival rates.[3,4] Glypicans constitute one of the two major families of heparin sulfate proteoglycans, with the other major family being syndecans.[5] Glypican-3 (GPC3), which is expressed mainly during pregnancy in fetal organs regulating morphogenesis, has been shown to be active in HCC development.[6] In early HCC, GPC3 is highly expressed, so it is a sensitive and specific biomarker for diagnosis, and monitoring of this protein can predict poor disease outcome.[7]

This study evaluated both S100A4 and GPC3 expression in primary HCC in relation to tumour aggressiveness and diagnosis. Tissues from 70 patients met the inclusion criteria for hepatectomy out of 400 cases of HCC in Egyptian cirrhotic hepatitis virus C (HCV) patients evaluated by immunohistochemistry

using antibodies against SA100A4 and GPC3 on the slides of tissue microarrays and these were compared to tumour-adjacent tissue (controls).[8] All patients were followed up for survival, local recurrence, and metastasis over a period of at least 6 months.

In HCC cells, GPC3 was more strongly expressed than S100A4 when both were compared to controls (79% and 21%, respectively). S100A4 was more significantly expressed in cases showing metastasis, vascular emboli, necrosis, and Grade III tumours, while no significant association with GPC3 expression was found with all these parameters. GPC3 expression was associated with the time of HCC recurrence; this correlation was not observed with S100A4 expression. The mean value of alpha-fetoprotein tumour marker was higher in both positive cases for S100A4 and GPC3, but in both S100A4 and GPC3-positive cases the overall survival time was not affected. These results indicated that S100A4 could be used as a prognostic marker for HCC progression because its expression is related to tumour metastasis, grading, and vascular invasion while GPC3 is a reliable marker of HCC diagnosis.

References

1. Kim JK et al. Targeted disruption of S100P suppresses tumor cell growth by down-regulation of cyclin D1 and CDK2 in human hepatocellular carcinoma. Int J Oncol. 2009;35(6):1257-64.
2. Cui JF et al. Identification of metastasis candidate proteins among HCC cell lines by comparative proteome and biological function analysis of S100A4 in metastasis in vitro. Proteomics. 2006;6(22):5953-61.
3. Liu Z et al. Clinicopathological significance of S100A4 expression in human hepatocellular carcinoma. J Int Med Res. 2013;41(2):457-62.
4. Helfman DM et al. The metastasis associated protein S100A4: Role in tumour progression and metastasis. Br J Cancer. 2005;92(11):1955-8.
5. Xiao WK et al. Prognostic significance of glypican-3 in hepatocellular carcinoma: A meta-analysis. BMC Cancer. 2014;14:104.
6. Wu Y et al. GPC-3 in hepatocellular carcinoma: Current perspectives. J Hepatocell Carcinoma. 2016;3:63-7.
7. Chen IP et al. Positive glypican-3 expression in early hepatocellular carcinoma predicts recurrence after hepatectomy. J Gastroenterol. 2014;49(1):117-25.
8. Staib F et al. CellMinerHCC: A microarray-based expression database for hepatocellular carcinoma cell lines. Liver Int. 2013;34(4):621-31.

Table 1: Logistic regression analysis of independent predictors for metastasis.

Independent predictor	Univariate regression			Multivariate regression	
	β	p	OR (95% CI)	p	AOR (95% CI)
S100A4 Negative (r) Positive	2.266	0.015*	9.63 (1.56–59.30)	0.041*	8.4 (1.08–49.80)
Necrosis No (r) Yes	2.120	0.048*	8.33 (1.08–75.60)	-	-
Size	-0.562	0.078	0.570 (0.300–1.060)	-	-
AST	-0.047	0.056	0.950 (0.900–1.001)	-	-
ALT	-0.097	0.05*	0.91 (0.82–1.00)	0.066	0.90 (0.80–1.01)
Constant Model chi-squared % correctly predicted	0.771 12.17, p=0.002 95.3%				

ALT: alanine aminotransferase; AOR: adjusted odds ratio; AST: aspartate transaminase; CI: confidence interval; COR: crude odds ratio.

Bowel Preparation for Small Bowel Capsule Endoscopy: Better Late than Never

Authors: *Bruno Rosa, Sofia Xavier, Sara Monteiro, Cátia Arieira, Rui Magalhães, Tiago Cúrdia Gonçalves, Joana Magalhães, Maria João Moreira, José Cotter

Gastroenterology Department, Hospital Senhora da Oliveira, Guimarães, Portugal; School of Medicine, University of Minho, Braga, Portugal; PT Government Associate Laboratory ICVS/3B's, Guimarães/Braga, Portugal
*Correspondence to bruno.joel.rosa@gmail.com

Disclosure: Dr Rosa has provided consultancy services for Medtronic and has a speaker services agreement with Jaba Recordati and Norgine. All additional authors report no conflicts of interest.

Keywords: Bowel preparation, capsule endoscopy, small bowel.

Citation: EMJ Gastroenterol. 2018;7[1]:76-77. Abstract Review No. AR5.

Since the turn of the millennium, small bowel capsule endoscopy (SBCE) has become the preferred method for investigating the small bowel, namely in cases of suspected mid-gastrointestinal bleeding or Crohn's disease. However, it remains somewhat controversial whether the patients should undergo bowel preparation for the procedure, and what is the best way of achieving better results in a convenient, safe, and well-tolerated manner. The classical recommendation from the manufacturer, still widely used to date, has been that patients receive a low-fibre diet the day before the procedure, with clear liquids only during the evening and 12 hours fast before capsule ingestion. However, recent meta-analyses have challenged this approach, by showing that the ingestion of a purgative solution, such as 2 L polyethylene glycol (PEG) prior to the examination could improve the quality of mucosal visualisation, and possibly also the diagnostic yield of SBCE.[1,2] The use of such a protocol has been recently recommended by the European Society of Gastrointestinal Endoscopy (ESGE), although the society stressed that the optimal timing for taking the purgatives is yet to be established.[3]

This uncertainty regarding timing inspired our study, wherein we aimed to evaluate three different protocols of bowel preparation for SBCE by comparing outcomes regarding quality of visualisation, diagnostic yield, small bowel transit time (SBTT), and completion rate. Protocol A was the classical protocol (no preparation); for protocol B, patients ingested 1 L of PEG/ascorbic acid (MoviPrep™, Bridgewater, New Jersey, USA) the evening before the examination; and protocol C patients ingested 1 L of PEG/ascorbic acid (MoviPrep) on the day of examination after the capsule passed the small bowel, as assessed with the Real Time Viewer function of the Data Recorder DR3 used for PillCam™ SB3 (Medtronic, Minneapolis, Minnesota, USA). We included 101 consecutive patients, randomised for the three protocols. SBCE videos were blindly reviewed by two experienced gastroenterologists who reported all relevant endoscopic findings and classified the quality of bowel preparation, according to the percentage of the examination with a clear view, as excellent (>90%), good (76–90%), fair (50–75%), or poor (<50%). Patients were mainly female (approximately two thirds), with a mean age of 47 years, and the main indications were suspected mid-gastrointestinal bleeding (41%) and suspected Crohn's disease (38%), with similar distribution among the three groups. The capsule was complete in 94.1% of patients, with a mean SBTT of 250±113 minutes, similar between the three protocols. For both readers, bowel preparation was good or excellent in a significantly higher proportion of patients in protocol C (approximately 75%), while in protocols B and A this was inferior to 45% and 40%, respectively. Looking at endoscopic findings, overall there were no differences in the diagnostic yield among the three protocols, although angioectasias were more prevalent in patients in protocol C (5.4%, 9.7%, and 27.3% of patients in groups A, B, and C, respectively).

Following the data's presentation, we were questioned about the tolerability of and adverse events associated with the bowel preparation. Conducting the preparation only during the

examination was well-tolerated, safe, and did not interfere with the previous day's activities or cause any sleep disturbance. In conclusion, the administration of 1 L of PEG/ascorbic acid, administered during the examination after the capsule reaches the small bowel, was associated with better mucosal visualisation, without affecting SBTT or the completion rate, and with a possible positive impact on diagnostic yield; thus, we suggest this innovative protocol should be used systematically as the standard protocol to improve SBCE results.

References

1. Wu S et al. Optimal use of polyethylene glycol for preparation of small bowel video capsule endoscopy: A network meta-analysis. Curr Med Res Opin. 2017;33(6):1149-54.
2. Kotwal VS et al. Should bowel preparation, antifoaming agents, or prokinetics be used before video capsule endoscopy? A systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2014;26(2):137-45.
3. Rondonotti E et al. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Technical Review. Endoscopy. 2018;50(4):423-46.

Outlet Dysfunction is Prevalent in Severe Functional Bloating: A Prospective, Multicentre, Italian Study

Authors: *Paola Iovino,[1] Maria Cristina Neri,[2] Lucia D'Alba,[3] Giuseppe Chiarioni[4]

1. University of Salerno, Salerno, Italy
2. Pio Albergo Trivulzio, Milan, Italy
3. Ospedale San Giovanni-Addolorata, Rome, Italy
4. Azienda Ospedaliera Universitaria Integrata (AOUI) Verona, Verona, Italy

*Correspondence to piovino@unisa.it

Disclosure: The authors have declared no conflicts of interest.

Keywords: Abdominal bloating, abdominal distension, balloon expulsion test, functional bloating, functional constipation, functional gastrointestinal disorders, irritable bowel syndrome.

Citation: EMJ Gastroenterol. 2018;7[1]:77-78. Abstract Review No. AR6.

Our research objective was to investigate the relationship between the defecation pattern, the severity of bloating, and the abdominal girth changes in patients with functional gastrointestinal disorders who reported bloating as their most common complaint. Bloating and abdominal distension, very common and bothersome symptoms, are associated with low treatment responsiveness.[1]

In this prospective, multicentre study spanning all areas in Italy, we enrolled patients with severe abdominal bloating as their prevalent complaint score (≥24 on a 0–100 mm Visual Analog Scale [VAS])[2] with or without visible abdominal distension.[3] The most common diagnoses according to Rome III criteria were irritable bowel syndrome (constipation subtype) and functional bloating. During the run-in, patients were invited to record a diary and measure abdominal girth at fasting and postprandially, as well as to be adherent to traditional irritable bowel syndrome dietary advice (i.e., NICE guidelines) augmented by a lactose-free diet. Patients who completed the run-in completed a questionnaire to assess subjective improvement of symptom perception on a 5-point Likert scale (from 'worse' to 'major improvement'), a further assessment of bloating on VAS, and girth measurement by investigators. Both bloating VAS and abdominal girth changes correlated with subjective improvement of symptom perception. Thirty-one percent of patients reported a clinical benefit from following simple dietary advice. The simplicity of a lactose-free diet supplemented by NICE advice was a key factor for the strong adherence of the patients to the protocol. Indeed, a low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet was more complex and did not show further benefit compared to NICE advice.[4] Only patients who did not report any improvement underwent a

standardised balloon expulsion test;[5] in most patients, this test was scored as a failure, showing that outlet dysfunction was prevalent in the non-responders group and related to bloating severity.

The aetiology of bloating and abdominal distension is still unclear. They may be produced by different mechanisms, for example, an impaired handling of bowel gaseous content by abdomino-phrenic dyssynergia has been recently demonstrated by studies from Barcelona.[6] An increased generation of intestinal gas inside the gut itself may produce bloating and distension.[7] Moreover, intestinal gas production depends on a summation effect of pre-existing fermentable substrates and recent colonic loads of fermentable foodstuffs.[8] This may explain why bloating strongly correlates with distention in patients with constipation.[9] However, there is a lack of solid data on defecation patterns in patients complaining of severe bloating, albeit dyssynergic defecation is a well-known cause of impaired evacuation of faecal material.

Recognising the different operative mechanisms that might be coincident in the same individual helps plan effective treatment. Our data might support bowel retraining as a potential treatment option for functional bloating and a biofeedback trial to improve defecation effort is also ongoing to better understand the relevance of outlet dysfunction as a contributing aetiology to functional bloating.

References

1. Neri L, Iovino P. Bloating is associated with worse quality of life, treatment satisfaction, and treatment responsiveness among patients with constipation-predominant irritable bowel syndrome and functional constipation. Neurogastroenterol Motil. 2016;28(4):581-91.
2. Cappello C et al. A randomised clinical trial (RCT) of a symbiotic mixture in patients with irritable bowel syndrome (IBS): Effects on symptoms, colonic transit and quality of life. Int J Colorectal Dis. 2013;28(3):349-58.
3. Iovino P et al. Bloating and functional gastro-intestinal disorders: Where are we and where are we going? World J Gastroenterol. 2014;20(39):14407-19.
4. Böhn L et al. Diet low in FODMAPs reduces symptoms of irritable bowel syndrome as well as traditional dietary advice: A randomized controlled trial. Gastroenterology. 2015;149(6):1399-407.
5. Chiarioni G et al. Validation of the balloon evacuation test: Reproducibility and agreement with findings from anorectal manometry and electromyography. Clin Gastroenterol Hepatol. 2014;12(12):2049-54.
6. Malagelada JR et al. Bloating and abdominal distension: Old misconceptions and current knowledge. Am J Gastroenterol. 2017;112(8):1221-31.
7. Guarner F, Malagelada JR. Gut flora in health and disease. Lancet. 2003;361(9356):512-9.
8. Mego M et al. Accumulative effect of food residues on intestinal gas production. Neurogastroenterol Motil. 2015;27(11):1621-8.
9. Houghton LA et al. Relationship of abdominal bloating to distension in irritable bowel syndrome and effect of bowel habit. Gastroenterology. 2006;131(4):1003-10.

Safety and Rate of Delayed Adverse Events with Lumen-Apposing Metal Stents for Pancreatic Fluid Collections: A Multicentre Study

Authors: Yaseen B. Perbtani, Peter V. Draganov, *Dennis Yang

Division of Gastroenterology and Hepatology, University of Florida, Gainesville, Florida, USA
*Correspondence to Dennis.Yang@medicine.ufl.edu

Disclosure: Dr Perbtani has declared no conflicts of interest. Dr Yang and Dr Draganov are consultants for Boston Scientific Corp. and Micro-Tech Endoscopy.

Keywords: Delayed adverse events (AE), lumen-apposing metal stents (LAMS), pancreatic fluid collections (PFC), pancreatic pseudocyst (PP), walled-off necrosis (WON).

Citation: EMJ Gastroenterol. 2018;7[1]:78-80. Abstract Review No. AR7.

Endoscopic transmural drainage of symptomatic pancreatic fluid collections (PFC) using lumen-apposing metal stents (LAMS) has become

common practice.[1] However, recent studies have raised concerns for potential delayed adverse events (AE) associated with prolonged indwelling LAMS, including delayed bleeding and the phenomenon of 'buried stent syndrome', in which extensive mucosal tissue overgrowth around the flanges of the stent compromises stent removal during follow-up.[2] Based on these observations, the current guidelines by the European Society of Gastrointestinal Endoscopy (ESGE) recommend the retrieval of LAMS within 4 weeks to prevent stent-related AE; however, the ESGE recognise that this is based on low-quality evidence.[3]

Establishing the incidence and type of delayed AE associated with LAMS has direct clinical ramifications on the follow-up strategy for patients with pancreatic walled-off necrosis (WON) and pancreatic pseudocyst (PP). The objective of our study was to perform a multicentre retrospective analysis to assess delayed AE with LAMS and to identify potential predictors of treatment failure and delayed AE.

A total of 122 patients (64 WON and 58 PP) underwent LAMS placement. There were no statistically significant differences in age, sex, BMI, or American Society of Anesthesiologists (ASA) grade between patients with WON versus those with PP. Successful LAMS insertion was achieved in 98% of patients in both groups (p=1.0). Mean size of PFC was similar for WON (131±44 mm) versus PP patients (95±48 mm; p=0.6). Follow-up imaging was performed at a median of 4 weeks after LAMS insertion. PFC resolution was significantly higher for PP patients (97%) compared with WON (62%) (p<0.001). Stent occlusion was the most common delayed AE identified (18% of PP patients and 30% of WON patients; p=0.13) at follow-up endoscopy performed at a median of 5 weeks after LAMS insertion. Overall, there was only one case of delayed self-limited bleeding at the time of stent removal, and in two patients the LAMS was partially buried but were retrieved without difficulty. A flow chart of the patients included in this study is depicted in Figure 1. Use of electrocautery-enhanced LAMS was the only factor associated with treatment failure of WON (objective response: 13.2; 95% confidence interval: 3.33–51.82; p=0.02) on logistic regression. There were no patient, operator, or procedure-related factors predictive of stent occlusion.

In summary, our study demonstrates that LAMS are safe and effective for the treatment of PFC. Delayed bleeding or buried stent syndrome was seldom seen in our study. Most cases of PP resolve within 4 weeks and, therefore, early stent removal can be achieved without compromising the efficacy of the intervention.

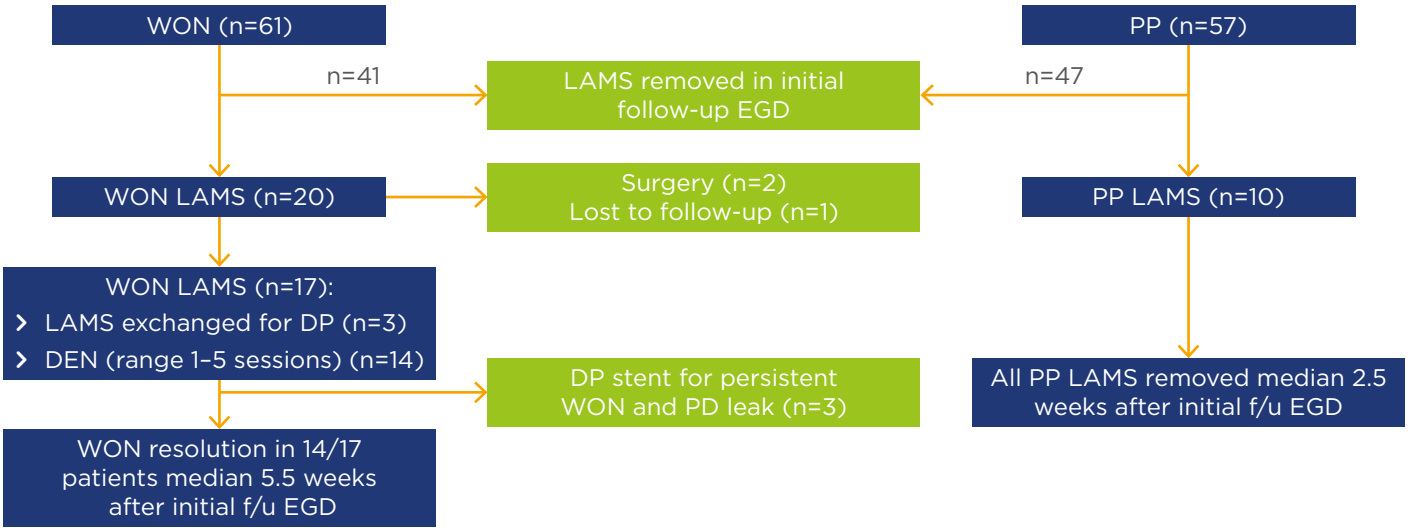


Figure 1: A flow chart of lumen-apposing metal stent removal and subsequent follow-up.

DEN: direct endoscopic necrosectomy; DP: double pigtail; EGD: esophagogastroduodenoscopy; f/u: follow-up; LAMS: lumen-apposing metal stents; PP: pancreatic pseudocyst; WON: walled-off necrosis.

Conversely, as shown in this study, many cases of WON persist at 4 weeks after LAMS placement and early stent removal may simply not be feasible for these patients. Given the current wide variation in clinical practice, particularly for patients with WON, we urgently need high-quality, controlled studies to evaluate the role and timing of adjunct strategies (e.g., endoscopic necrosectomy, additional stenting through LAMS, multigate drainage) that may expedite PFC resolution and facilitate early LAMS removal.

References

1. Mussetto A et al. Current uses and outcomes of lumen-apposing metal stents. Ann Gastroenterol. 2018;31(5): 535-40.
2. Bang JY et al. Non-superiority of lumen-apposing metal stents over plastic stents for drainage of walled-off necrosis in a randomised trial. Gut. 2018. [Epub ahead of print].
3. Arvanitakis M et al. Endoscopic management of acute necrotizing pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) evidence-based multidisciplinary guidelines. Endoscopy. 2018;50(5): 524-46.

Acetic Acid-Guided Biopsies Versus Mapping Biopsies for Barrett's Surveillance: The ABBA Study

Authors: *Gaius Longcroft-Wheaton, Pradeep Bhandari

Portsmouth Hospitals NHS Trust, Portsmouth, UK
*Correspondence to gaiuslw@gmail.com

Disclosure: The authors have declared no conflicts of interest.

Keywords: Acetic acid, Barrett's, cancer, chromoendoscopy, dysplasia, high-grade dysplasia (HGD), neoplasia, surveillance.

Citation: EMJ Gastroenterol. 2018;7[1]:80-81. Abstract Review No. AR8.

Barrett's surveillance currently involves untargeted mapping biopsies; however, this procedure can still miss certain pathologies.[1] Acetic acid (AA) can be used to identify neoplasia for targeted biopsy[2] but has not previously been studied in a surveillance population.

We performed a multicentre, randomised, crossover feasibility study to compare neoplasia detection with AA-targeted biopsies and untargeted mapping biopsies in a Barrett's surveillance population with no history of dysplasia or cancer. All patients underwent two gastroscopies 8 weeks apart, one with AA-guided biopsy of abnormal areas only (Portsmouth protocol) and one using the Seattle protocol for mapping biopsies. The neoplasia yield (low-grade dysplasia [LGD], high-grade dysplasia [HGD], and cancer) and number of biopsies taken with each strategy were evaluated. Recruitment and retention were assessed and qualitative telephone interviews were conducted. Qualitative sampling continued until data saturation was attained; thematic analysis was used.

Recruitment comprised six UK centres and 200 patients, with a mean age of 66 years (standard deviation: 11.1). A total of 145 participants were male and the mean Barrett's length was C4M6; 192 participants completed at least one procedure, with 175 completing both. The neoplasia prevalence was 11 out of 192 (5.8%). All cases of HGD and cancer were found with both protocols, with a full breakdown shown in Table 1. All LGD patients underwent further gastroscopy, with no neoplastic changes found in any of the cases during follow-up. Using the Seattle protocol, 2,139 biopsies were taken, with a pathology cost of £125,987 (306 biopsies per neoplasia, with a cost of £18,023). In contrast, 226 biopsies were taken with the Portsmouth protocol, equating to a total cost of £13,311 (75 biopsies per neoplasia, with a cost of £6,656). This represented a 4-fold difference in the number of biopsies per neoplasia. On restricting analysis to HGD and cancer, 1,070 biopsies were required per lesion found using the Seattle protocol and 113 biopsies per

lesion found using the Portsmouth protocol, which represented a 9.5-fold difference.

For the qualitative study, we interviewed 21 participants to achieve data saturation, 6 non-participants, and 6 clinicians (1 per UK centre). Participants found the AA procedure simple and quick, with less pain and soreness experienced post-procedure. They felt the technique could potentially give more immediate results, providing reassurance or leading to more rapid treatment. Clinicians found the technique easy to implement following training[3] and noted decreased discomfort for patients.

This was the first randomised controlled trial to compare these two techniques and it was reassuring that no cases of HGD or cancer were missed with either technique. LGD remains controversial[4] and we believe inflammation could have resulted in a false–positive LGD result within this cohort, since subsequent gastroscopy and biopsies did not reveal LGD in any of the cases. A huge reduction in the number of biopsies can reduce the cost and time required for the procedure; therefore, these feasibility data support a definitive trial of AA-targeted biopsies in Barrett's surveillance.

This UEG Week presentation generated considerable discussion. Delegates were surprised at the high level of retention in the study, with 88% of patients completing both endoscopies. It was questioned whether a randomised trial rather than a crossover design could have been used, but the qualitative data supported this design because it is the safest way of avoiding missed pathologies. It was questioned whether advances in endoscope resolution and advanced imaging technologies would render AA chromoendoscopy obsolete. However, it was recognised that, to date, there have been no studies comparing effectiveness of these techniques in Barrett's surveillance, and from an international perspective, it will be some time before there is universal adoption of new equipment, which is currently very expensive. AA can be used with any endoscope, making the technology universally available.

References

1. Kariv R et al. The Seattle protocol does not more reliably predict the detection of cancer at the time of esophagectomy than less invasive surveillance protocol. Clin Gastroenterol Hepatol. 2009;7(6):653-8.
2. Longcroft-Wheaton G et al. Acetic acid spray is an effective tool for the endoscopic detection of neoplasia in Barrett's esophagus. Clin Gastroenterol Hepatol. 2010;8(10):843-7.
3. Chedgy FJQ et al. Development and validation of a training module on the use of acetic acid for the detection of Barrett's neoplasia. Endoscopy. 2017;49(2):121-9.
4. Vennalaganti P et al. Discordance among pathologists in the United States and Europe in diagnosis of low-grade dysplasia for patients with Barrett's esophagus. Gastroenterology. 2017;152(3):564-70.

Table 1: Breakdown of diagnoses by protocol.

	Metaplasia or no biopsy taken	LGD	HGD	Cancer	Total
Portsmouth protocol	171	1	1	1	174
Seattle protocol	168	4	1	1	174
Both protocols	NA	1	1	1	3
Total histology	166	6	1	1	174

HGD: high-grade dysplasia; LGD: low-grade dysplasia; NA: not applicable.

VIEW MORE ABSTRACTS ONLINE ←

Mechanisms Underlying Chemotherapy-Associated Mucositis: The Role of Inflammatory Mediators and Potential Therapeutic Targets

EDITOR'S PICK

Mucositis is an undesirable side effect experienced by cancer patients during chemotherapy and characterised by both inflammation and loss of cells from the epithelial barrier of the gastrointestinal tract. This fascinating article from Menezes-Garcia et al. reviews the inflammatory mechanisms behind chemotherapy's toxic effect on the gastrointestinal tract and discusses the potential therapeutic targets that can contribute to mucositis treatment and prevention. This interesting and highly relevant paper will no doubt add to the debates in this field.

Samantha Warne

Editor

Authors: *Zelia Menezes-Garcia,[1] Raquel Duque do Nascimento Arifa,[2] Caio Tavares Fagundes,[3] Danielle Gloria Souza[4]

1. Department of Microbiology and Department of Biochemistry, University of Texas Southwestern Medical Center, Dallas, Texas, USA
2. Departments of Pathology and Medicine, Skirball Institute of Biomolecular Medicine, New York University School of Medicine, New York City, New York, USA
3. Centro de Pesquisa e Desenvolvimento de Fármacos, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil
4. Laboratório de interação Micro-organismo-Hospedeiro, Departamento de Microbiologia, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

*Correspondence to biomenezel@gmail.com

Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: The authors are grateful to Celso M. Queiroz-Junior for his help with Figure 1.

Received: 12.10.17

Accepted: 30.08.18

Keywords: Chemotherapy, gastrointestinal (GI) tract, inflammation, mucositis.

Citation: EMJ Gastroenterol. 2018;7[1]:82-91.

Abstract

Chemotherapy-induced mucositis is a common, often severe, side effect experienced by cancer patients during their treatment, which is a major challenge for successful anticancer therapy. As chemotherapy regimens evolve to include more efficacious agents, mucositis is increasingly becoming a major cause of dose-limiting toxicity and merits further investigation. This condition is characterised by both inflammation and loss of cells from the epithelial barrier of the gastrointestinal tract. This article reviews the current understanding of the inflammatory mechanisms behind chemotherapy's toxic effect on the gastrointestinal tract and provides evidence that inflammation

is a key factor behind gastrointestinal toxicity of chemotherapy. The authors discuss potential therapeutic targets that can contribute to mucositis treatment and prevention.

MUCOSITIS AS A MAJOR CHALLENGE FOR SUCCESSFUL ANTICANCER THERAPY

Mucositis is one of the most undesired side effects of antineoplastic chemotherapeutic and/or radiotherapeutic treatments.[1] This condition is characterised by both inflammation and loss of cells from the epithelial barrier of the gastrointestinal (GI) tract. Clinically, mucositis is associated with various symptoms, such as severe GI pain, nausea, bleeding, severe diarrhoea, and starvation, which can lead to a reduction or interruption of antitumour treatment.[2] All of these complications result in longer hospitalisation, increased cost to the healthcare system, and increased risk of mortality.

The current model for the development of mucositis suggests that there are five intertwined phases: initiation, upregulation and generation of messenger signals, signal amplification, ulceration, and healing (Figure 1).[2] Briefly, in the initial phase, chemotherapy damages the DNA of epithelial cell progenitors and induces intense oxidative stress and cell death. In the second and third phases, there is an increase in cellular apoptosis and a progressive loss of cells from the crypt and the absorptive surface. An influx of inflammatory cells and increased production of inflammatory mediators in the mucosa are also hallmarks of these three phases. These events amplify the damaging process and lead to epithelial erosion. In the fourth stage, there is ulceration of the epithelium. This may result in the invasion of the submucosa layer by the indigenous microbiota and exacerbation of the inflammatory process. Changes in microbiota composition are common during mucositis development, resulting in dysbiosis,[1,3] and they are important for the pathogenesis of mucositis. The last step is the recovery, in which cessation of the application of chemotherapy leads to restoration of the GI structure.[4] Some of the molecular mechanisms involved in the progression of these pathologic phases have recently been described and will be detailed in the following sections of this manuscript, focussing on the contribution of inflammatory mediators to the progression of mucositis.

INFLAMMATORY MECHANISMS ASSOCIATED WITH THE AMPLIFICATION OF TISSUE INJURY DURING CHEMOTHERAPY-INDUCED MUCOSITIS

Mechanisms involved in mucositis pathogenesis are complex and are not limited to the direct epithelial damage induced by chemotherapy.[5] Sonis et al.[6] demonstrated that there is marked endothelial cell injury following exposure of the oral mucosa to antineoplastic therapy. This event precedes any detectable changes in the epithelium.[6] Other studies have provided evidence that damage to GI stem cells is a consequence of extensive microvascular injury.[7] Wherever the primary site of cellular injury, both culminate in the promotion of inflammation, a prominent component in mucosal damage during antineoplastic therapy, as highlighted in the model for mucositis development depicted above.[1] Some of the molecular mechanisms involved in the progression of each of these steps are discussed below.

Reactive Oxygen Species and Inflammasomes

According to the model introduced by Sonis et al.,[2] the primary inducer involved in unleashing mucosal injury upon chemotherapy is the production of reactive oxygen species (ROS), which is secondary to the chemotherapy-induced DNA damage. ROS are believed to cause direct cellular damage and tissue injury due to modifying several cellular structures.[8] Hence, the authors have demonstrated that there is intense oxidative stress during irinotecan-induced mucositis in mice.[9] This oxidative stress was shown to be dependent on NADPH-oxidase (NOX) activity, as Gp91phox-deficient mice and other animals models treated with a NOX inhibitor reverted irinotecan-induced oxidative stress. Importantly, NOX inhibition, by genetic or pharmacologic approaches, was able to prevent inflammation progression and mucositis development in the gut upon irinotecan treatment, implicating NOX2-derived ROS in chemotherapy-induced mucositis.

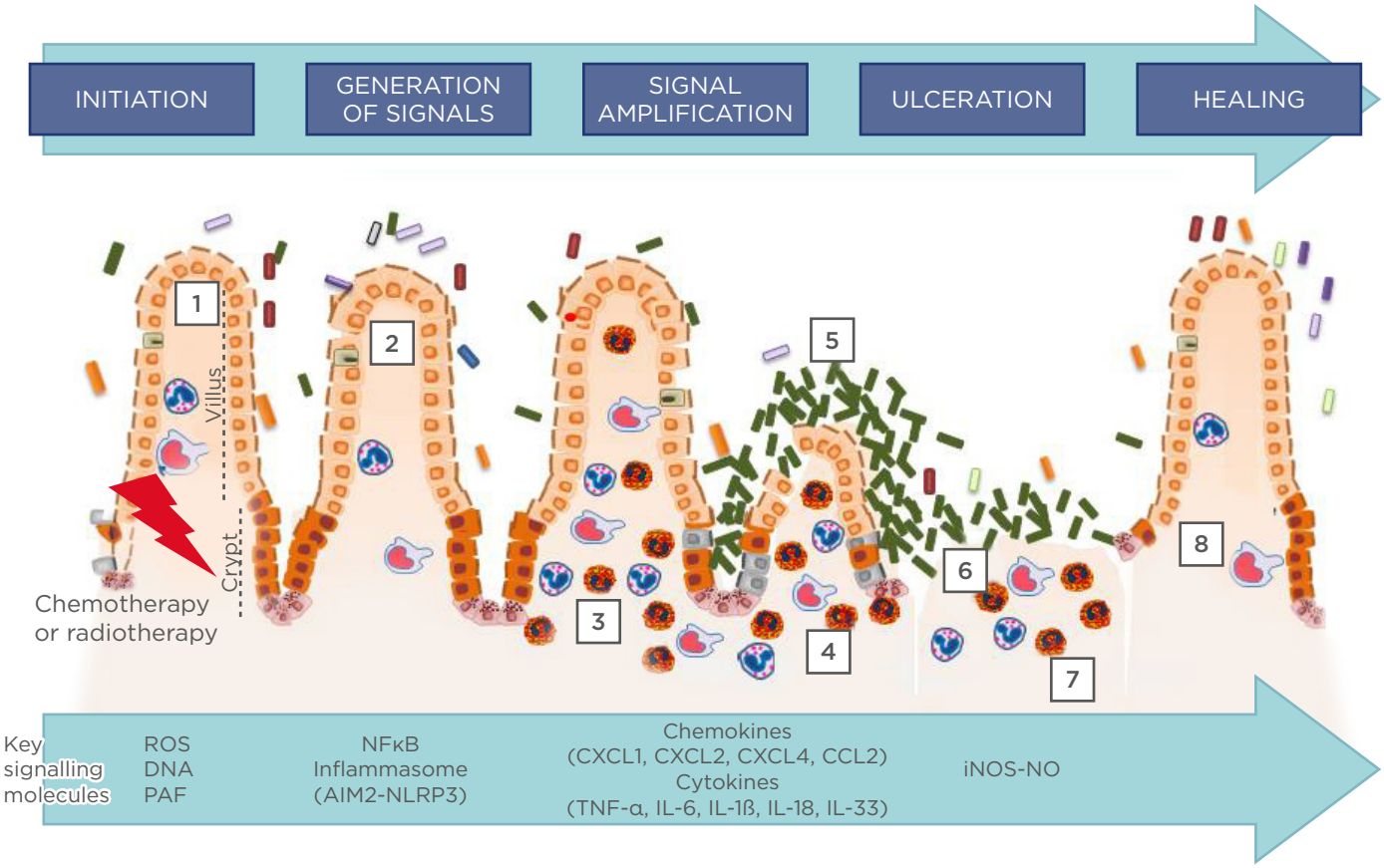


Figure 1: Current model of the pathophysiology of mucositis.

According to the current model, five phases are important in the pathophysiology of mucositis: 1) The generation of ROS, and DNA release from damaged cells and lipids mediators, like PAF during the initiation phase; 2) Activation of NFκB and inflammasome multiprotein assembly, followed by the induction of messenger molecules, such as TNF-α, IL-6, and CXCL1; 3) Treatment-related tissue inflammation and apoptosis during the upregulation/message generation phase, characterised by neutrophil, eosinophil, and macrophage influx to the lamina propria; 4 and 5) Microbiota-induced NFκB and inflammasome multi-protein assembly, via PAMP, which contributes to amplification of inflammation. The enhanced production of messenger molecules in the amplification and signalling phase, triggered by cytokine signalling, leukocyte influx, and dysbiotic microbiota, culminates in heightened inflammation and apoptosis (3 and 4), and discontinuity of the epithelial barrier resulting from apoptosis during the ulcerative phase (6), thereby promoting bacterial translocation (7). A spontaneous healing phase is initiated after chemotherapy cessation (8), characterised by intense cell proliferation.

iNOS-NO: inducible isoform nitric oxide synthase; NO: nitric oxide; PAF: platelet activating factor; PAMP: pathogen-associated molecular patterns; ROS: reactive oxygen species.

Adapted from Sonis.[2]

In addition to NOX2-expressing leukocytes, it was demonstrated that enterocytes are a source of ROS production after chemotherapy and that the treatment of mice with the ROS scavenger fullerol leads to diminished inflammation and disease manifestation in irinotecan-treated mice.[10] Other work has suggested that NOX1 plays an important role in the pathogenesis of 5-fluorouracil (5FU)-induced intestinal mucositis.[11] In NOX1-deficient mice, the severity of mucositis was significantly reduced, particularly with respect to crypt disruption. This result was associated with attenuated production of ROS when compared to wild-type mice. NOX1-derived ROS production following administration of 5FU promotes the apoptotic response through upregulation of inflammatory cytokines.[11] Radiation-induced mitochondrial dysfunction and ROS production were also shown to be involved in oral mucositis promotion in rats and preventing mitochondrial ROS production with melatonin was effective

in preventing mucositis development.[12] Altogether, these findings support the idea that chemotherapy-induced ROS production by several sources leads to tissue inflammation and mucositis induction.

The mechanisms involved in ROS-mediated amplification of the inflammatory response during chemotherapy-induced mucositis are still under investigation, but two pathways play major roles: the activation of NFκB and assembly of the multiprotein complexes called inflammasomes. Hence, chemotherapy and radiotherapy treatment are able to activate NFκB in epithelial cells, mesenchymal cells, endothelial cells, and macrophages, and its activation is believed to be secondary to chemotherapy-induced oxidative stress.[1] NFκB plays a central role in triggering multiple proinflammatory signalling pathways, such as cytokine and chemokine synthesis.[1,13,14] In this regard, Logan et al.[13] demonstrated that expression and activation of NFκB precedes the peak of proinflammatory cytokine production in chemotherapy-induced mucositis. In another study, mice treated with a NFκB inhibitor showed diminished tissue damage, decreased IL-1β production, and neutrophil accumulation in the bowel after administration of 5FU.[14] These findings reinforce the hypothesis that NFκB activation is central to the mucosal inflammation induced by chemotherapy and radiotherapy.

ROS production during chemotherapy also activates inflammatory mediator production through activation of the multiprotein complex inflammasome. Inflammasome assembly involves the oligomerisation of several proteins, including NOD-like receptors, such as NLRP3; adaptor proteins, such as ASC; and inflammatory caspases, such as caspase-1. The activation of this complex leads to induction of the caspase activity and the maturation of IL-1β and IL-18.[15] In murine models, there is marked inflammasome activation in the gut, which is assessed by increased cleaved caspase-1 levels upon irinotecan-induced mucositis induction. NOX2-derived ROS were necessary for inflammasome activation in this system.[9] Also, in radiation-induced oral mucositis, mitochondria-derived ROS are involved in NLRP3 inflammasome activation.[12] Importantly, mice deficient for the ASC and caspase-1 inflammasome components were protected from mucositis development after irinotecan treatment,[9] implicating this pathway in the amplification of inflammation and tissue injury during chemotherapy-induced mucositis. The cytokines IL-1β and IL-18 are well-known NFκB activators,[16] implying that ROS-driven NFκB activation may be, in part, dependent on inflammasome assembly. Therefore, inflammasome activation seems to be pivotal for chemotherapy-induced mucositis.

Another implication for the inflammasome pathway in mucositis has been shown by Lian et al.,[17] who highlighted the activation of AIM2 by genomic DNA released from the intestine. Double-strand DNA from germinative cells of the intestine is secreted in exosomes after irinotecan treatment; this DNA promotes IL-1β and IL-18 maturation in an AIM2-dependent manner, leading to mucositis and diarrhoea. Abrogation of AIM2 signalling, either in AIM2-deficient mice or by a pharmacological inhibitor, such as thalidomide, significantly reduces the incidence of drug-induced diarrhoea.[17]

Cytokines

It has been demonstrated that several proinflammatory cytokines and chemokines play prominent roles in the pathogenesis of mucositis. Several studies have shown elevated production of the inflammasome-dependent cytokines IL-1β and IL-18 during clinical and experimental chemotherapy-induced mucositis.[9,16,18-21] In fact, the deficiency for IL-18 or treatment with IL-18BP or IL-1RA (which block IL-18 and IL-1 activity, respectively), resulted in a marked reduction in tissue inflammation and mucositis development.[9,16-20] Furthermore, antibody neutralisation of IL-1 also prevented mucositis and epithelial tight junction dysfunction and alleviated mucositis in mice.[16]

In addition to promoting inflammation, IL-1β enhances mucositis development by triggering apoptosis of intestinal crypt epithelial cells via p53-mediated upregulation of p21 and p27.[16] IL-1β apoptotic activity was blocked by IL-1RA administration.[16] Altogether, these findings provide compelling evidence that IL-1β and IL-18 production are of pivotal importance for mucositis development.

IL-33, secretion of which is influenced by inflammasome activation, is produced by the intestinal epithelial cells of mice treated

with irinotecan. Treatment of mice with an anti-IL-33 antibody or IL-33 receptor antagonist or deletion of the receptor for this cytokine resulted in attenuation of intestinal injury after chemotherapeutic intervention.[21]

In addition to inflammasome-derived cytokines, other inflammatory cytokines, such as TNF-α, IL-6, IL-4, and the chemokines CXCL1, CXCL2, CXCL4, and CCL2, are also associated with the development of intestinal mucositis induced by chemotherapy.[18,21-26] Hence, inhibition of TNF-α and CXCL1 production with pentoxifylline or thalidomide resulted in a decrease in the pathogenesis of mucositis induced by irinotecan.[18] Furthermore, knockout of IL-4 efficiently prevented the pathological alterations of 5FU-induced mucositis in the duodenum of the mice.[18]

CXCL1, CXCL2, and CCL2 are induced during mucositis in an IL-33-dependent pathway and promote neutrophil and macrophage recruitment, respectively, to the mucosa of the small intestine.[21] CXCL4 and its receptor CXCR3 were confirmed, at both the genomic and protein level, to be regulated during 5FU-induced mucositis.[24] CXCL4 neutralising monoclonal antibody decreased the incidence, severity, and duration of chemotherapy-induced diarrhoea and reduced apoptosis of the crypt epithelia by suppression of the 5FU-induced expression of p53 and BAX through its receptor, CXCR3. CXCL4 activates the phosphorylation of p38 MAPK, which mediates the stimulated expression of p53 and BAX, and results in the ultimate activation of caspase-8, 9, and 3.[24] Therefore, CXCL4, through activation of CXCR3 receptor, fosters mucositis development by favouring epithelial cell apoptosis. Altogether, the above-detailed studies reinforce the concept that different types of proinflammatory cytokines might be important to the establishment of mucositis by maintaining and amplifying the inflammatory response.

In addition to cytokines, some studies have demonstrated the involvement of platelet activating factor (PAF), a leukocyte-mobilising lipid mediator in mucositis.[27,28] Hence, patients with oral mucositis showed increased levels of PAF in the saliva.[27] Mice-deficient for the PAF receptor were protected from 5FU-induced mucositis, with reduced production of TNF-α, CXCL1, and IL-1β,[28] suggesting that this mediator might be involved in recruitment of the cells responsible for production of these proinflammatory mediators.

Leukocytes

Chemotherapy-induced cytokines and chemokines promote large infiltration of leucocytes into the lamina propria.[1,9,20,29,30] More recent studies have confirmed that neutrophils,[20] eosinophils (Arifa et al., manuscript in preparation), and macrophages[21] play an important role in the pathogenesis of mucositis.

Several studies have indicated that neutrophil accumulation in the gut during mucositis contributes to tissue injury.[9,18,21,23,25] Guabiraba et al.[21] showed that neutrophils are highly activated in the blood 3 days after irinotecan treatment in mice. The concentration of CXCL1 was elevated in the serum at the same time. Furthermore, neutrophils accumulated in the small intestine were found to express the CXCR2 chemokine receptor. In addition, it was shown that inhibition of neutrophil influx into the intestine during treatment with irinotecan, by anti-Ly6G antibody or CXCR2 antagonism, resulted in attenuation of inflammation and intestine injury.

In addition, several studies have indicated that inhibition of cytokine action is associated with a reduced neutrophil accumulation in the gut during mucositis, thereby reducing tissue damage.[9,18,20,21,23,25] Pentoxifylline, a methylxanthine derivative that reduces the expression of TNF-α, IL-1β, and IL-8, was associated with reduced myeloperoxidase activity and injury in the small intestine following chemotherapy-induced mucositis.[18,23] Similar results were found by this group for thalidomide, an inhibitor of TNF-α production. IL-18, IL-33, or caspase-knockout mice or IL-18BP treatment clearly decreased neutrophil influx and injury in the intestine,[20,21] as well as IL-1RA treatment in irinotecan-induced mucositis.[9] Altogether, these results evidence that granulocyte recruitment to the mucosa during mucositis plays an essential role in tissue injury and disease development.

In addition to granulocytes, there is evidence to suggest that macrophages perform an important role in chemotherapy-induced mucositis.[20] The number of F4/80-positive macrophages

was markedly increased in irinotecan-treated mice. Moreover, these cells were identified as the major producers of IL-18 in the mucosa after irinotecan treatment. Taking these findings into consideration, it is reasonable to suggest that both granulocytes and macrophages are key agents for the pathology underlying chemotherapy-induced mucositis.

The nitric oxide (NO) synthases (NOS) plays a relevant role in the mucositis pathogenesis.[23,31-33] This enzyme converts L-arginine and oxygen into L-citrulline and NO. NO is an important effector molecule produced by neutrophils and macrophages.[34] Cytokines have been shown to stimulate the expression of the inducible NOS isoform 2 (NOS2) with consequent production of NO. This gas has antimicrobial activity and immune modulating and cytotoxic action toward the adjacent host tissues,[35] resulting in pain, tissue lesions, and apoptosis.[36-38] In radiotherapy and chemotherapy-induced mucositis, there are increases in NOS2 enzyme expression and activity in both the intestine and mouth mucosa.[23,31,32,39] Additionally, mice treated with aminoguanidine, a selective NOS2 inhibitor, and NOS2-knockout mice have shown a reduction in radiotherapy and chemotherapy-induced mucositis due to reduced NO production.[23,39] In summary, NO, released by neutrophils and macrophages, contributes to upregulation of inflammation and chemotherapy-induced injury.

INVOLVEMENT OF THE INTESTINAL MICROBIOTA IN MUCOSITIS

The authors and other research groups have demonstrated that host ability to mount an appropriate inflammatory response upon tissue injury is dependent on the intestinal bacterial colonisation.[40-43] Germ-free (GF) mice are more resistant to radiotherapy and chemotherapy-induced mucositis;[44-46] hence, GF mice are markedly resistant to lethal radiation and irinotecan-induced mucositis, and have shown a reduced number of apoptotic cells compared to conventional mice.[44-46] GF mice treated with irinotecan presented with a reduced neutrophil and eosinophil accumulation and reduced levels of proinflammatory cytokines in the intestine, such as IL-1β and TNF-α, compared to irinotecan-treated conventional mice.[46] These results suggest that the intestinal microbiota plays a key role in increasing chemotherapy and radiotherapy-induced intestinal toxicity, a phenotype that might be explained by the known modulatory role played by the microbiota over host inflammatory responsiveness[41,43] or by directly exacerbating tissue injury induced by antineoplasic treatment due to bacterial colonisation of eroded intestinal tissue.

Based on the Sonis mucositis model, colonisation of the eroded mucosa by bacteria, fungi, and viruses occurs mainly at the ulceration phase and precedes secondary infections.[2,6] Indeed, there is a higher abundance of microbiota in the ulcerated epithelium compared to the intact epithelium.[47] These findings suggest that bacteria present on the ulcer surface are active contributors to the mucositis process.

However, only 8% of new patients with cancer will be at high risk of developing ulcerative mucositis. The majority of the new cancer patients are in the intermediate-risk category of developing mucositis, in which on average between 20% and 49% will develop ulcerative mucositis.[6] Intestinal microbiota may be important contributors not only to the ulcerative phase of mucositis but also to the other stages of the disease.[33,48] Furthermore, products of bacteria, such as metabolites and pathogen-associated molecular patterns (PAMP), may exert a chemotactic activity on leukocytes and stimulate them to further secrete proinflammatory cytokines, which does not depend on mucosa ulceration. PAMP are subject to innate immune monitoring by pattern recognition receptors. For example, cell wall components, such as lipopolysaccharide and β-glucan or flagellar components, are recognised as PAMP and trigger proinflammatory and antimicrobial responses in immune cells.[49] The sensing of microbial products by these sentinel receptors could be involved in mucositis progression.

Indeed, some pattern recognition receptors, such as Toll like-receptor (TLR)2, 4, 5, and 9, and the receptors involved in inflammasome activation were reported to be involved in the pathogenesis of mucositis.[9,17,33,50-52] TLR2, TLR9, and MyD88 signalling have also been implicated in doxorubicin and irinotecan-induced mucositis in mice; mice deficient for TLR2 and MyD88 expression were protected from mucositis

development.[33,53] TLR4 expression in the gut is induced upon administration of 5FU in the mouse model,[54] but whether TLR4 activation is involved in mucositis progression has not been evaluated. Treatment with TLR5 agonists during radiotherapy decreased numbers of apoptotic cells in the GI mucosa, alleviated mucositis development, and improved survival of mice and primates.[55,56] These studies strongly suggest that TLR5 activation by exogenous agonist administration is efficient at protecting the gut mucosa from damage. Altogether, these findings suggest that TLR and their activators, such as PAMP, play an important role in mucositis pathogenesis.

Changes in the microbiota, called dysbiosis, might promote dysregulation of the immune system.[57-59] Dysbiosis also plays a relevant role in chemotherapy-associated mucositis.[48,60] Several studies have demonstrated that chemotherapeutics exert a detrimental effect on the intestinal microbial composition. Shifts in microbiota composition differ along the GI tract and according to the chemotherapy regimen.[3,9,61] Overall, dysbiosis during anticancer treatments leads to a reduction in the diversity and richness of the bacterial community.[62] These alterations in microbiota composition usually coincide with the development of chemotherapy-induced mucositis in humans and in animal models.[3] Altogether, these studies demonstrate that there are major changes in the microbiota during chemotherapy-induced mucositis and these shifts are potentially involved in the development of mucosal tissue injury.

There is evidence that the indigenous microbiota impact the development of chemotherapy-mediated mucositis. Some of the mechanisms involved in disease promotion by the gut microbial community are still under evaluation, but it is plausible to suggest that dysbiotic microbiota and their structural andmetabolic products foster mucositis development, at least in part, by amplifying the inflammatory mechanisms responsible for tissue injury progression.

POTENTIAL THERAPEUTIC TARGETS FOR MUCOSITIS TREATMENT

A better understanding of the pathogenesis of chemotherapy or radiation-induced mucositis is required to develop and implement optimal preventive and curative approaches for patients with this condition. Overall, the studies discussed so far provide extensive evidence that inflammation takes a central role in the pathogenesis of chemotherapy-induced mucositis. The knowledge gathered from these studies support the idea that interfering in inflammatory pathways may be efficient at alleviating mucositis development (Table 1[9,10,14,18,20,21,27,31]) in a time-specific manner.

In this context, ROS, PAF, and NFκB inhibition are potential therapeutic targets during the initial phases of mucositis. As demonstrated in Figure 1, ROS and PAF, followed by the activation of NFκB, are the first signals released after the start of the chemotherapy or radiotherapy treatment. Several antioxidant agents have recently been investigated in the prevention of mucositis.[63-65] A recent study has shown that the antioxidant N-acetyl cysteine was efficient at decreasing the frequency of severe oral mucositis in patients.[63] Therapeutic targeting of these molecules may prevent the triggering of the entire response that leads to mucositis.

In addition, inhibition of the inflammasomes or the actions of their derived cytokines, IL-1β and IL-18, may prevent mucositis development in the second phase. Inhibiting cytokines and chemokines is a potential therapeutic strategy, especially at subsequent steps. Indeed, a nonsteroidal anti-inflammatory drug, benzydamine, that inhibits the production of proinflammatory cytokines such as IL-1β and TNF-α, is recommended for prevention of oral mucositis during anticancer treatment.[66] Drugs targeting IL-1β and TNF-α are available, having been approved for use in other conditions, and could provide initial targets for alleviating inflammatory alterations during mucositis. Intervening in the recruitment of leukocytes and their effector molecules (NOS2 and NO) may also have a beneficial effect, but only in later stages of the disease and may have little effect on the maintenance of the initial events of the disease.

However, some anti-inflammatory compounds, such as pentoxifylline and misoprostol, were inefficient at preventing mucositis.[66] These results clearly suggest that the medical community is far from comprehensively understanding this complex toxic side effect.

Table 1: Therapeutic targets that have been tested for the treatment of experimental intestinal mucositis in mice.

Phase of mucositis	Target	Pharmacological approach	Mechanism of action
Phase I Arifa et al.,[10] 2016	ROS	Fullerol	ROS scavenger
Phase I Arifa et al.,[9] 2014	NADPH-oxidase derived ROS	Apocynin	NADPH-oxidase inhibitor
Phase I McManus et al.,[27] 1993	PAF	Antagonism of PAFR	PAFR antagonist
Phase II Chang et al.,[14] 2012	NFκB	5-ASA	NFκB inhibitor
Phase III Arifa et al.,[9] 2014; Lima-Júnior et al.,[20] 2014	IL-18	IL-18BP	Prevents binding of IL-18 to its receptor
Phase III Arifa et al.,[9] 2014	IL-1β	IL-1RA	IL-1 receptor antagonist
Phase III Melo et al.,[18] 2008; Lima-Júnior et al.,[23] 2012	Cytokines	Pentoxifylline	Reduces expression of TNF-α, IL-1β, and CXCL1
Phase III Melo et al.,[18] 2008; Lima-Júnior et al.,[23] 2012	TNF-α	Thalidomide	Inhibits TNF-α production
Phase III Guabiraba et al.,[21] 2014	IL-33	Anti-IL-33 antibody	Prevents binding to the ST2 receptor
Phase III Guabiraba et al.,[21] 2014	IL-33	sST2 recombinant	Soluble IL-33 receptor prevents binding of IL-33 to the ST2 receptor
Phase IV Guabiraba et al.,[21] 2014	Neutrophils	DF-2156A	CXCR2 antagonist inhibits neutrophil recruitment
Phase IV Lima-Júnior et al.,[20] 2014; Carvalho et al.,[30] 2017	NOS2	Aminoguanidine or L-NAME	NOS2 inhibitor

NOS: nitric oxide synthase; PAF: platelet activating factor; PAFR: platelet activating factor receptor; ROS: reactive oxygen species.

A possible explanation for this discrepancy may be the dual effect played by inflammatory signalling during anticancer treatment: it is important for both the side effects and some of the tumouricidal properties of chemotherapy and radiotherapy, such as mucositis. Future research must also evaluate whether inflammatory molecules have an effect on the tumouricidal activity of the relevant chemotherapeutic drugs; a subject that will impact the translation of the findings discussed here to the clinic.

Finally, by influencing the expression and release of immune effector molecules, the maintenance of commensal intestinal microbiota is a potential target for homeostasis and health in the intestinal tract during anticancer therapy. Indeed, several studies have demonstrated the beneficial effects exerted by probiotics, symbiotics, and prebiotics in rodent models and in humans.[66] In conclusion, the studies involving mucositis have highlighted several potential therapeutic targets. However, it is still necessary to advance these studies to allow new findings to be applied in clinical treatments.

References

1. van Vliet MJ et al. Chemotherapy treatment in pediatric patients with acute myeloid leukemia receiving antimicrobial prophylaxis leads to a relative increase of colonization with potentially pathogenic bacteria in the gut. Clin Infect Dis. 2009;49(2): 262-70.
2. Sonis ST. The pathobiology of mucositis. Nat Rev Cancer. 2004;4(4):277-84.
3. Stringer AM et al. Chemotherapy-induced modifications to gastrointestinal microflora: Evidence and implications of change. Curr Drug Metab. 2009;10(1):79-83.
4. Duncan M, Grant G. Oral and intestinal mucositis - Causes and possible treatments. Aliment Pharmacol Ther. 2003;18(9):853-74.
5. Ribeiro RA et al. Irinotecan- and 5-fluorouracil-induced intestinal mucositis: Insights into pathogenesis and therapeutic perspectives. Cancer Chemother Pharmacol. 2016;78(5):881-93.

6. Sonis ST. New thoughts on the initiation of mucositis. Oral Dis. 2010;16(7):597-600.
7. Paris F et al. Endothelial apoptosis as the primary lesion initiating intestinal radiation damage in mice. Science. 2001;293(5528):293-7.
8. Di Meo S et al. Role of ROS and RNS sources in physiological and pathological conditions. Oxid Med Cell Longev. 2016;2016:1245049.
9. Arifa RD et al. Inflammasome activation is reactive oxygen species dependent and mediates irinotecan-induced mucositis through IL-1β and IL-18 in mice. Am J Pathol. 2014;184(7):2023-34.
10. Arifa RDN et al. The reduction of oxidative stress by nanocomposite Fullerol decreases mucositis severity and reverts leukopenia induced by Irinotecan. Pharmacol Res. 2016;107:102-10.
11. Yasuda M et al. Potential role of the NADPH oxidase NOX1 in the pathogenesis of 5-fluorouracil-induced intestinal mucositis in mice. Am J Physiol Gastrointest Liver Physiol. 2012;302(10):G1133-42.
12. Ortiz F et al. Melatonin blunts the mitochondrial/NLRP3 connection and protects against radiation-induced oral mucositis. J Pineal Res. 2015;58(1):34-49.
13. Logan RM et al. Nuclear factor-κB (NF-κB) and cyclooxygenase-2 (COX-2) expression in the oral mucosa following cancer chemotherapy. Oral Oncol. 2007;43(4):395-401.
14. Chang CT et al. 5-Fluorouracil induced intestinal mucositis via nuclear factor-κB activation by transcriptomic analysis and in vivo bioluminescence imaging. PLoS One. 2012;7(3):31808.
15. Amaral FA et al. NLRP3 inflammasome-mediated neutrophil recruitment and hypernociception depend on leukotriene B4 in a murine model of gout. Arthritis Rheum. 2012;64(2):474-84.
16. Wang X et al. IL-1Ra selectively protects intestinal crypt epithelial cells, but not tumor cells, from chemotoxicity via p53-mediated upregulation of p21(WAF1) and p27(KIP1.). Pharmacol Res. 2014; 82:21-33.
17. Lian Q et al. Chemotherapy-induced intestinal inflammatory responses are mediated by exosome secretion of double-strand DNA via AIM2 inflammasome activation. Cell Res. 2017;27(6):784-800.
18. Melo ML et al. Role of cytokines (TNF-α, IL-1β and KC) in the pathogenesis of CPT-11-induced intestinal mucositis in mice: Effect of pentoxifylline and thalidomide. Cancer Chemother Pharmacol. 2008;61(5):775-84.
19. Wu ZQ et al. Interleukin-1 receptor antagonist reduced apoptosis and attenuated intestinal mucositis in a 5-fluorouracil chemotherapy model in mice. Cancer Chemother Pharmacol. 2011;68(1):87-96.
20. Lima-Júnior RC et al. Targeted inhibition of IL-18 attenuates irinotecan-induced intestinal mucositis in mice. Br J Pharmacol. 2014;171(9):2335-50.
21. Guabiraba RA et al. IL-33 targeting attenuates intestinal mucositis and enhances effective tumor chemotherapy in mice. Mucosal Immunol. 2014;7(5):1079-93.
22. Logan RM et al. Is the pathobiology of chemotherapy-induced alimentary tract mucositis influenced by the type of mucotoxic drug administered? Cancer Chemother Pharmacol. 2009;63(2):239-51.
23. Lima-Júnior RC et al. Involvement of nitric oxide on the pathogenesis of irinotecan-induced intestinal mucositis: Role of cytokines on inducible nitric oxide synthase activation. Cancer Chemother Pharmacol. 2012;69(4):931-4.
24. Gao J et al. Activation of p38-MAPK by CXCL4/CXCR3 axis contributes to p53-dependent intestinal apoptosis initiated by 5-fluorouracil. Cancer Biol Ther. 2014;15(8):982-91.
25. Soares PM et al. Inflammatory intestinal damage induced by 5-fluorouracil requires IL-4. Cytokine. 2013;61(1):46-9.
26. de Araújo RF Jr et al. Olmesartan decreased levels of IL-1β and TNF-α, down-regulated MMP-2, MMP-9, COX-2, RANK/RANKL and up-regulated SOCs-1 in an intestinal mucositis model. PLoS One. 2014;9(12):e114923.
27. McManus LM et al. Radiation-induced increased platelet-activating factor activity in mixed saliva. Lab Invest. 1993;68(1):118-24.
28. Soares PM et al. Role of platelet-activating factor in the pathogenesis of 5-fluorouracil-induced intestinal mucositis in mice. Cancer Chemother Pharmacol. 2012;68(3):713-20.
29. Handschel J et al. Increase of RM3/1-positive macrophages in radiation-induced oral mucositis. J Pathol. 2001;193(2):242-7.
30. Carvalho RD et al. Secretion of biologically active pancreatitis-associated protein I (PAP) by genetically modified dairy Lactococcus lactis NZ9000 in the prevention of intestinal mucositis. Microb Cell Fact. 2017;16(1):27.
31. Leitão RF et al. Role of nitric oxide on pathogenesis of 5-fluorouracil induced experimental oral mucositis in hamster. Cancer Chemother Pharmacol. 2007;59(5):603-12.
32. Leitão RF et al. Role of inducible nitric oxide synthase pathway on methotrexate-induced intestinal mucositis in rodents. BMC Gastroenterol. 2011;16(11):90.
33. Wong DVT et al. The adaptor protein Myd88 is a key signaling molecule in the pathogenesis of irinotecan-induced intestinal mucositis. PLoS One. 2015;10(10):e0139985.
34. Bogdan C. Nitric oxide synthase in innate and adaptive immunity: An update. Trends Immunol. 2015;36(3):161-78.
35. Kröncke KD et al. Nitric oxide: Cytotoxicity versus cytoprotection – How, why, when, and where? Nitric Oxide. 1997;1(2):107-20.
36. Estrada C et al. Nitric oxide mediates tumor necrosis factor-alpha cytotoxicity in endothelial cells. Biochem Biophys Res Commun. 1992;186(1):475-82.
37. Kendall HK et al. Nitric oxide and tissue destruction. Oral Dis. 2001;7(1):2-10.
38. Laurent M et al. Kinetic modelling of the nitric oxide gradient generated in vitro by adherent cells expressing inducible nitric oxide synthase. Biochem J. 1996;314(Pt 1):109-13.
39. Moura JF et al. A novel model of megavoltage radiation-induced oral mucositis in hamsters: Role of inflammatory cytokines and nitric oxide. Int J Radiat Biol. 2015;91(6):500-9.
40. Souza DG et al. The required role of endogenously produced lipoxin A4 and annexin-1 for the production of IL-10 and inflammatory hyporesponsiveness in mice. J Immunol. 2007;179(12):8533-43.
41. Souza DG et al. The essential role of the intestinal microbiota in facilitating acute inflammatory responses. J Immunol. 2004;173(6):4137-46.
42. Amaral FA et al. Commensal microbiota is fundamental for the development of inflammatory pain. Proc Natl Acad Sci U S A. 2008;105(6):2193-7.
43. Fagundes CT et al. Transient TLR activation restores inflammatory response and ability to control pulmonary bacterial infection in germfree mice. J Immunol. 2012;188(3):1411-20.
44. Crawford PA, Gordon JI. Microbial regulation of intestinal radiosensitivity. Proc Natl Acad Sci U S A. 2005;102(37):13254-9.
45. Brandi G et al. Intestinal microflora and digestive toxicity of irinotecan in mice. Clin Cancer Res. 2006;12(4):1299-307.
46. Pedroso SH et al. Evaluation of mucositis induced by irinotecan after microbial colonization in germ-free mice. Microbiology. 2015;161(10): 1950-60.
47. Rand KH et al. Cancer chemotherapy

associated symptomatic stomatitis: Role of Herpes simplex virus (HSV). Cancer. 1982;50(7):1262-5.

48. van Vliet MJ et al. The role of intestinal microbiota in the development and severity of chemotherapy-induced mucositis. PLoS Pathog. 2010;6(5):e1000879.
49. Medzhitov R. Recognition of microorganisms and activation of the immune response. Nature. 2007;449(7164):819-26.
50. Thorpe DW et al. Chemotherapy-induced mucositis: The role of the gastrointestinal microbiome and toll-like receptors. Exp Biol Med (Maywood). 2013;238(1):1-6.
51. Cario E et al. Toll-like receptor 2 controls mucosal inflammation by regulating epithelial barrier function. Gastroenterology. 2007;132(4): 1359-74.
52. Krieg AM. CpG motifs in bacterial DNA and their immune effects. Ann Rev Immunol. 2002;20:709-60.
53. Kaczmarek A et al. Severity of doxorubicin-induced small intestinal mucositis is regulated by the TLR-2 and TLR-9 pathways. J Pathol. 2012;226(4):598-608.
54. Ferreira TM et al. Oral supplementation of butyrate reduces mucositis and intestinal permeability associated with 5-Fluorouracil administration. Lipids. 2012:47(7):669-78.
55. Burdelya LG et al. An agonist of toll-like receptor 5 has radioprotective activity in mouse and primate models. Science. 2008;320(5873):226-30.
56. Burdelya LG et al. Toll-like receptor 5 agonist protects mice from dermatitis and oral mucositis caused by local radiation: Implications for head-and-neck cancer radiotherapy. Int J Radiat Oncol Biol Phys. 2012;83(1):228-34.
57. Elinav E et al. NLRP6 inflammasome regulates colonic microbial ecology and risk for colitis. Cell. 2011;145(5):745-57.
58. Maslowski KM et al. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. Nature. 2009;461(7268):1282-6.
59. Brown EM et al. The role of the immune system in governing host-microbe interactions in the intestine. Nat Immunol. 2013;14(7):660-7.
60. Stringer AM et al. Chemotherapy-induced mucositis: The role of gastrointestinal microflora and mucins in the luminal environment. J Support Oncol. 2007;5(6):259-67.
61. Von Bültzingslöwen I et al. Oral and intestinal microflora in 5-fluorouracil treated rats, translocation to cervical and mesenteric lymph nodes and effects of probiotic bacteria. Oral Microbiol Immunol. 2003;18(5): 278-84.
62. Touchefeu Y et al. Systematic review: The role of the gut microbiota in chemotherapy- or radiation-induced gastrointestinalmucositis – Current evidence and potential clinical applications. Aliment Pharmacol Ther. 2014;40(5):409-21.
63. Moslehi A et al. N-acetyl cysteine for prevention of oral mucositis in hematopoietic SCT: A double-blind, randomized, placebo-controlled trial. Bone Marrow Transplant. 2014;49(6):818-23.
64. Tsujimoto T et al. L-glutamine decreases the severity of mucositis induced by chemoradiotherapy in patients with locally advanced head and neck cancer: A double-blind, randomized, placebo-controlled trial. Oncol Rep. 2015;33(1):33-9.
65. Chattopadhyay S et al. Role of oral glutamine in alleviation and prevention of radiation-induced oral mucositis: A prospective randomized study. South Asian J Cancer. 2014;3(1):8-12.
66. Lalla RV et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer. 2014;120(10):1453-61. Erratum in: Cancer. 2015;121(8):1339.

Adenoma and Malignant Colorectal Polyp: Pathological Considerations and Clinical Applications

Authors: *Emil Salmo,[1] Najib Haboubi[2]

1. Department of Histopathology, The Pennine Acute Hospitals NHS Trust, The Royal Oldham Hospital, Oldham, UK
2. University Hospital of South Manchester (Withington) and Trafford General Hospital, Manchester, UK

*Correspondence to emilsalmo@hotmail.com

Disclosure: The authors have declared no conflicts of interest.

Received: 20.07.18

Accepted: 28.09.18

Keywords: Adenoma, cancer, colon, polyp.

Citation: EMJ Gastroenterol. 2018;7[1]:92-102.

Abstract

Colon cancer remains one of the leading causes of cancer-related morbidity and mortality worldwide and it is generally accepted that most colorectal cancers arise from precursor adenomatous polyps. Malignant colorectal polyps should be resected en bloc, if possible, to facilitate thorough evaluation by the pathologist. This review will discuss the important parameters of malignant polyps that are prognostically important, with special emphasis on the pathological assessment of these polyps, which is important for planning further management and treatment strategies for patients.

INTRODUCTION

The word polyp simply means mucosal protrusion and it carries clinical significance only if the pathologist attaches a histopathological label. The polyp could be inflammatory, hamartomatous, serrated (hyperplastic), or neoplastic (dysplastic). Polyps assume one of two classical appearances: pedunculated polyps, which protrude for >2-fold the thickness of the adjacent mucosa and have a base smaller than one-third of the diameter of the head of the lesion; or sessile polyps, which have a base and top of the lesion that are approximately the same width. The term subpedunculated polyps is used by some specialists; these polyps are intermediate broad-based lesions that are dealt with in the same way as sessile lesions.[1,2]

Malignant colorectal polyps (MCRP) are common enough to warrant special attention and, with the introduction of bowel cancer screening programmes worldwide, large numbers of these polyps are being detected. Results have indicated that up to 50% of screen-detected cancers are identified in the early stages of disease progression.[3,4] This article details the frequency, malignant potential of adenomas, and pathological assessment of MCRP.

EPIDEMIOLOGY OF ADENOMAS

The prevalence of colorectal adenoma in a post mortem series ranged (female to male) from 14–20% in the <54 year-old group; 20–34% in the 55–64 year group; 35–44% in the 65–74 year group; and 33–52% in the >75 years

group, with the prevalence increasing with age.[5] The prevalence of MCRP in a series of endoscopically removed polyps was between 0.2% and 11.0%.[6]

In the clinical setting, there are various statistics linking the prevalence of adenoma with cancer. Of the first 1 million individuals screened in the NHS bowel cancer screening programme in England, >17,000 patients had a positive faecal occult blood test result. Of these, 1,574 (9%) were diagnosed with cancer, of whom 155 (10%) had polyp cancer.[1] Seventy-one percent of cancers were 'early' (32% Dukes A and 30% Dukes B) and 77% were left-sided, (29% rectal and 45% sigmoid). Only 14% of the cancers were right-sided, compared with expected figures of 67% and 24% for left and right-sided cancers, respectively, from the UK cancer registration.

The traditional question about the natural progression of adenoma was partly answered by the Mayo clinic group;[7] when they radiologically followed cohorts of patients with adenoma of ≥10 mm, they found that after 5 years there was 2.5% risk of malignant transformation, which increased to 8.0% after 10 years and 24.0% after 20 years. A limitation of this study is that there was no prior histological identification of the polyp type and they were assumed to be adenomatous.

POLYP HANDLING

Appropriate handling and assessment of polypectomy specimens in the laboratory is important for adequate interpretation of data, which ultimately affects patient management. To achieve optimal preparation, once the polyp is removed, it should be received fresh, pinned onto a cork board, and left to fix for at least 24 hours. Serial slicing along the stalk will ensure satisfactory assessment. Examination at a minimum of three levels is also beneficial and highly recommended. Exact identification of different sites by placing the polyps in separate containers is also recommended. From the personal experience of the authors, in some cases there is a variance between the endoscopic assessment as pedunculated and the pathological assessment as sessile. In such cases, this is probably the result of the endoscopists not taking out the entire stalk.

ADENOMA ARCHITECTURE

Adenomas are histologically divided into tubular, tubulovillous, or villous types according to the World Health Organization (WHO) 25% classification rule.[8] At least 25% of the volume of an adenoma should be villous to be classified as a tubulovillous adenoma and 75% villous to be defined as a villous adenoma.[8]

The 25% rule only applies to fully excised polyps, when the entire polyp can be assessed on the slide. In cases of small and fragmented lesions or superficial polyp biopsies, the presence of any identifiable villous component would classify the polyps as tubulovillous.[3,8]

ASSESSMENT OF ADENOMA SIZE

Size is one of the most important risk factors for malignant transformation in an adenoma. Nusko et al.[9] have shown that the incidence of polyp cancer is up to 40% in polyps >25 mm and up to 75% when the size reaches 35 mm. In the same series, the incidence of carcinoma in a polyp was around 11%.[9] In addition, increasing polyp size was seen to correlate with other adverse features, such as villous morphologyand high-grade dysplasia.

In a study of 13,992 asymptomatic patients undergoing screening colonoscopy, correlation of increasing size with adverse features was confirmed, with the proportion of advanced histology (villous morphology, high-grade dysplasia, or an invasive cancer) cases being 1.7% in the 1–5 mm group, 6.6% in the 6–9 mm group, and 30.6% in polyps >10 mm.[10] In view of the association with clinical outcome, polyp size is one of the factors used in decision-making regarding the need for future surveillance and assessing further management strategies. Polyp size is usually an objective parameter that is best assessed by the pathologist, because inaccurate size estimation can adversely affect a patient's management. Histological assessment of the size on the slide, as opposed to endoscopic measurement, is preferable because it is auditable, accurate, and simple to perform unless hampered by specimen fragmentation.

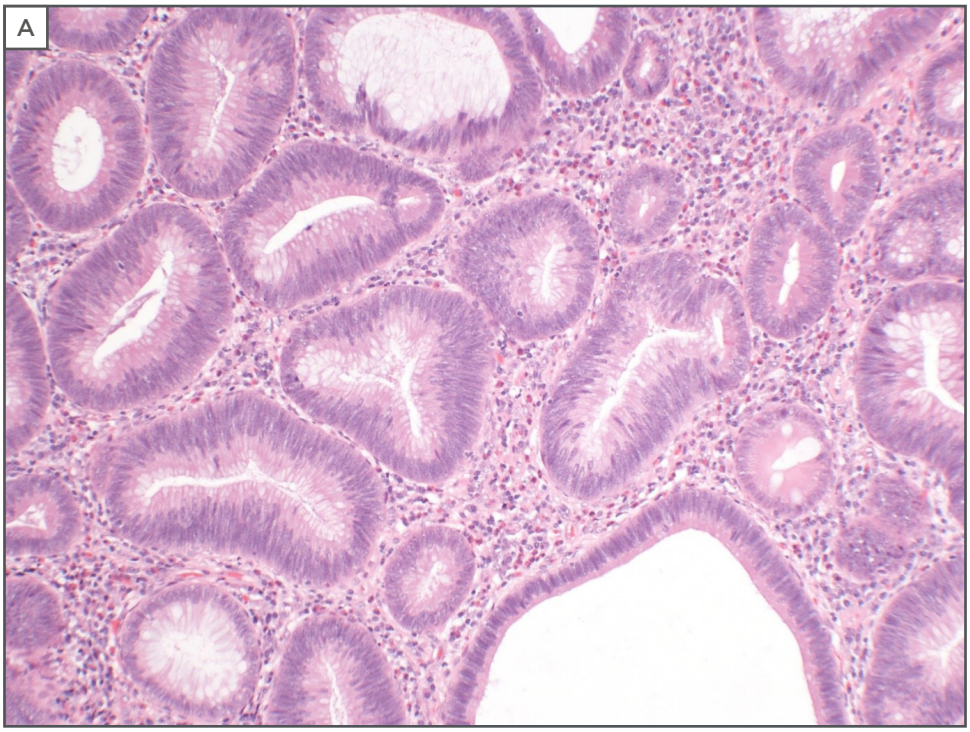


Figure 1A: Features of low-grade epithelial dysplasia with mild cellular stratification of glands.

The glands show evidence of low-grade dysplasia, with mild cellular stratification of glands and no evidence of complex architecture.

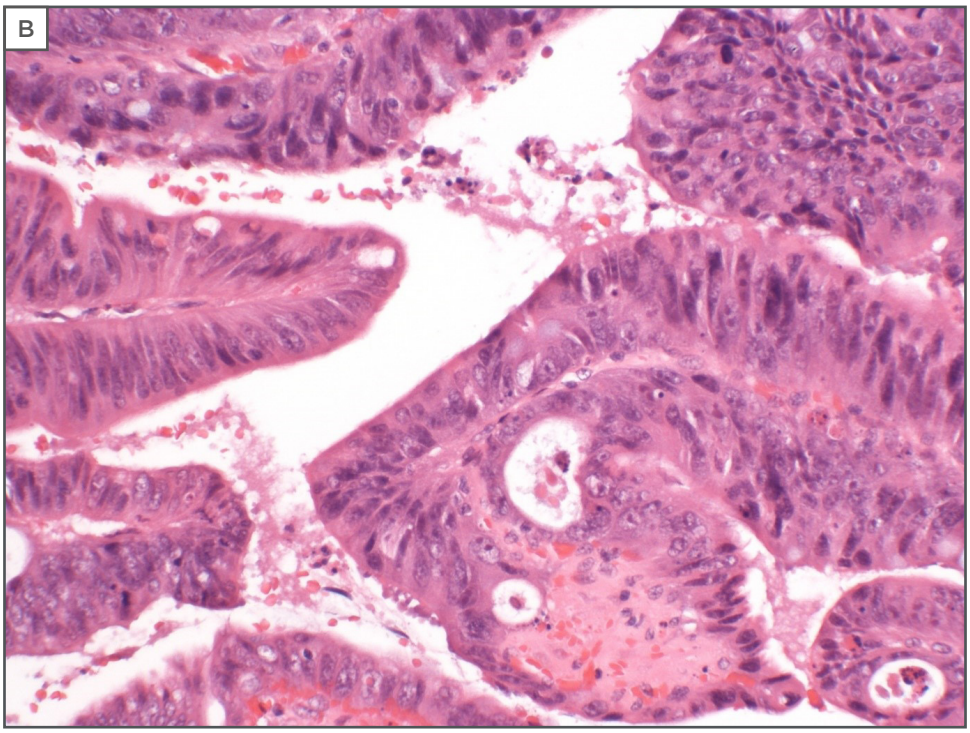


Figure 1B: Features representing high-grade dysplasia with prominent cellular stratification and complex glandular architecture.

The glands show more evident cellular stratification, with hyperchromatic nuclei and more complex architecture.

Levene et al.[11] conducted a study including 235 adenomtous polyps, of which 89% of adenomas had a documented endoscopic measurement and 22% a pathological measurement; the median endoscopic measurement was significantly greater, resulting in 13% of patients being misclassified as high or low risk, adversely affecting surveillance strategy.

Measuring the largest diameter on the haematoxylin and eosin-stained slide to the nearest millimetre is currently the most accurate assessment, and this should involve measuring the dysplastic component of a polyp excluding any normal component and normal stalk. If the specimen is received fragmented, it should be specifically stated in the report as not assessable and endoscopic measurements should be considered.[3,12,13]

GRADING OF EPITHELIAL DYSPLASIA

All adenomas are dysplastic by definition, and dysplasia is defined as epithelial changes that are unequivocally neoplastic.[14] Grading of dysplasia in adenomas should be exercised according to the revised Vienna classification of gastrointestinal epithelial neoplasia, using the two-tiered system of low and high-grade dysplasia.[15]

Low-grade dysplasia is an unequivocal neoplastic condition confined to the epithelial glands and this should be differentiated from inflammatory or regenerative changes.[14] High-grade dysplasia, in contrast to low-grade dysplasia, is characterised by complex glandular crowding and irregularity, prominent glandular budding, cribriform architecture, and 'back-to-back' glands with luminal papillary tufting (Figure 1A and Figure 1B).

High-grade dysplasia in an adenoma is a risk factor for frank malignant transformation, but there are exceptions to this rule because sometimes invasive carcinoma arises from low-grade dysplasia. However, it is standard to use the term malignant polyp on malignancy complicating adenomas and this is the term the authors will use in this paper. Although there are other forms of malignant polyps, like metastatic tumours, specifically malignant melanoma, neuroendocrine tumours, and various connective tissue cancers, including stromal tumours and polypoidal lymphomas, these are more rare. This paper will focus on malignancy complicating adenoma.

A number of studies have shown good concordance for the recognition of adenomatous features, but much lower levels of agreement for the assessment of histological type and grade of dysplasia, with interobserver variability higher among general pathologists than specialist gastrointestinal pathologists.[16,17]

ADVANCED ADENOMA

Advanced adenoma refers to adenomatous polyps that are either ≥10 mm in size, containing high-grade dysplasia, or villous in architecture, since these polyps are at a higher risk of malignant transformation. The term advanced adenoma should be avoided in pathology reports, and instead the pathologist should accurately describe each of the high-risk features, especially high-grade dysplasia, since increasing size is closely linked with the presence of high-grade dysplasia and is the most practical determinant of subsequent colorectal cancer risk.[3,12,17,18]

MALIGNANT COLORECTAL POLYPS

MCRP are adenomatous polyps in which cancer has developed and invaded through the muscularis mucosae (which acts as a protective biological basement membrane) into the submucosa. The lamina propria has a limited effective network of blood vessels and lymphatics, and, hence, invasion within the lamina propria does not carry metastatic risk; however, once the neoplasm breaches the muscularis mucosa into the submucosa, to be in a region rich with lymphatic and vascular channels, the metastatic risk becomes a real clinical threat.[19]

The experienced endoscopist can strongly suspect or even accurately diagnose MCRP from the following parameters: large and/or flatter polyps, ulceration, firmness, Paris Type 0–IIc, Kudo pit pattern type V, lateral non-granular spreading, or non-lifting. These parameters are not available to the pathologist and often it is a surprise diagnosis.[20]

HIGH-RISK HISTOLOGICAL FACTORS FOR REGIONAL AND DISTANT METASTASIS IN MALIGNANT COLORECTAL POLYPS

The overall frequency of lymph node metastasis in MCRP is around 10%;[21,22] once the diagnosis of MCRP is established, the risk of local and distant spread depends on certain risk factors.[23-25] A study by Hassan et al.[23] looked at looked at pooled data from 1,900 cases in 31 studies and assessed risk factors and their associations and found that poor differentiation, including signet ring pattern, was associated with increased mortality, positive resection margin associated with presence of residual disease, and lymphovascular invasion with high nodal metastasis. However, there is often a combination of these factors. Beaton et al.[26] added tumour budding and depth of invasion of >1 mm as risk factors for lymph node metastasis. In addition, Haggitt level 4 and Kikuchi level 2 and 3 of invasion have been found to carry risks for loco-regional and distant metastasis.[27,28]

HISTOLOGICAL TUMOUR TYPE AND DIFFERENTIATION

It is estimated that >95% of colorectal cancers are adenocarcinomas[29] and the conventional adenocarcinoma is characterised by glandular formation, which is the basis for tumour grading. Signet ring cell carcinoma has stage-independent adverse prognostic significance relative to conventional type adenocarcinoma, including mucinous adenocarcinoma, which has a better prognosis.[8]

Tumour grade and differentiation is regarded as a stage-independent prognostic factor; thus, high-grade or poorly differentiated tumours are associated with poorer prognosis.[8] Between 4 and 7% of MCRP show poor differentiation and this is usually an indication, combined with other factors, for surgery as the risk for nodal involvement is up to 70%.[23] There is a lack of universally agreed criteria for assessing poor differentiation and several guidelines recommend that when any area of the lesion shows poor differentiation, the tumour should be regarded as poorly differentiated.[3,13] The Royal College of Pathologists (RCPath) states that poor differentiation should be based on the worst area until the situation is clarified by further research.[13]

RESECTION MARGIN

Involvement of the resection margin in MCRP represents an adverse outcome and is considered a high risk factor.[12,13,30] Involvement of the mucosal margin may necessitate further local excision, while involvement of the deep stromal margin is usually an indication for a wider surgical excision. There is considerable discussion in the literature on the status of the margin clearance and what is considered acceptable to classify the tumour as completely excised. Most of the guidelines on this issue recommend that clearance of ≤1 mm signifies a positive and involved margin and is considered a higher risk factor.[3,13] In a recent study, Lopez et al.[30] showed that the outcomes following polypectomy in patients with a pathological margin ≥1 mm were similar to those following surgery in the general population. In the same study, the authors recommended that endoscopic resection needs to be completed by surgery if pathological margins are <1 mm[30] and other studies have also shown that resection was more likely to follow polypectomy if polypectomy margins were positive.[25,31]

EXTENT OF TUMOUR INVASION (STAGING)

There are several staging systems devised to assess the depth of tumour invasion in a MCRP, since increasing depth of invasion has been associated with adverse effects and higher risk of lymph node involvement. The most commonly used systems to date are those devised by Kikuchi et al.[27] and Haggitt et al.,[28] although other systems have been used on a smaller scale, such as those investigated by Kudo,[32] Ueno et al.,[33] and Nascimbeni et al.[34] In pT1 MCRP, the frequency of lymph node metastasis in sessile tumours that involve the superficial, middle, and deep thirds of the submucosa (Kudo and Kikuchi levels sm1, sm2, and sm3, respectively) has been reported to be 2%, 8%, and 23%, respectively.[27,34] On the other hand, in polypoid tumours, the level of invasion into the stalk of the polyp has been identified as

important in predicting outcome. For example, Haggitt[28] found that 'level 4' invasion, in which the tumour extended beyond the stalk of the polyp into the submucosa, but not into the muscularis propria, was an adverse factor. However, neither Kikuchi nor Haggitt systems are easy to use in practice and can both be subjective. The Haggitt level is particularly difficult to use in polypoid specimens lacking a clearly defined stalk ('sub-pedunculated') or if the specimen is poorly orientated. The Kikuchi method is not suitable for assessing samples in which the muscularis propria is not present. In addition, these systems depend on the subjective assessment of the pathologist, hence it is liable to significant observer variation.

Ueno et al.,[33] in their study of 292 patients with early invasive cancer, proposed that assessment of the width and depth of tumour invasion in millimetres is a better predictor of clinical outcome. They showed that when submucosal invasion width was <4 mm, the incidence of nodal metastasis was 2.5%. However, incidence of nodal metastasis was 18.2% when the width was ≥4 mm. When the submucosal invasion depth was <2 mm, the incidence of nodal involvement was 3.9%, but was 17.1% when the depth was ≥2 mm. Work from the Oxford Group[35] showed significant interobserver variation among pathologists when measuring polyp width using Ueno's staging method. However, the study highlighted a better agreement in measuring the depth of invasion and the researchers concluded that Ueno's method has the advantage of being independent of polyp morphology.

The authors' research group investigated 56 cases of polyps thought to be endoscopically benign but were malignant.[36] Four gastrointestinal pathologists scored the slides independently according to an agreed proforma and the results were collated. Significant variation in the assessment of agreed-upon important prognostic parameters using the various published staging systems was observed.[27,28,33] There was poor or fair agreement on the assessment of histological differentiation, Haggitt levels, lymphovascular invasion, and width of invasion measured in millimetres, similar to findings in other studies.[37] The best agreement was in the assessment of tumour invasion depth in millimetres according to Ueno classification. The conclusion that none of the staging systems used are suitable for all polyp types or had good reproducibility was drawn, leading to the recommendation to use all suitable systems when reporting MCRP samples.

There is an urgent need to make pathological assessment of MCRP easier and more reproducible; however, the authors recommend that pathologists adhere to agreed parameters and apply them rigidly while also making use of more than one staging system.

LYMPHOVASCULAR INVASION

The other important issue is the problem of combining lymphatic and vascular invasion under the term lymphovascular invasion. Although in simple haematoxylin and eosin stains it is more often than not the pathologist who finds it difficult to differentiate lymphatic from venous channels, the combination approach lacks scientific credibility as the final destination of the lymphatic drainage is different from venous drainage, with totally different clinical outcomes and requiring different therapeutic applications. The authors have argued along these lines[38] and suggested that the use of the currently available immunohistochemical stains (e.g., podoplanin and CD34) to differentiate lymphatic from venous and vascular invasions would significantly advance our knowledge in this area.

TUMOUR BUDDING

Tumour budding is an established independent prognostic factor in colorectal cancer but a standardised method for its assessment has been lacking. In the literature, tumour budding is defined as isolated single cancer cells or small clusters (<5 cells) of cancer cells at the infiltrating edge of the tumour and when there are 5 or more buds per 20 power field.[33] Studies of part 1 cancers have shown that the presence of tumour budding is associated with increased frequency of lymph node metastasis and also correlates with other adverse histological features.[26,33] This was confirmed by a recent study that showed that the presence of a higher number of tumour budding foci is associated with an increased risk of nodal metastasis.[25]

There are various methods in the literature to report and assess tumour budding and there is no one preferred or recommended method to

define budding, including the use of immunostains; hence, routine reporting of tumour budding is currently not recommended as standard.[12,13] This is despite a report from the International Tumour Budding Consensus Conference (ITBCC), which was established to find standardised criteria to define this phenomenon.[24] The overall consensus of the meeting supported the strong evidence for this important prognostic parameter and proposed that this method be incorporated into colorectal cancer guidelines/protocols and staging systems.

PITFALLS IN THE PATHOLOGICAL ASSESSMENT OF MALIGNANT COLORECTAL POLYPS

The main issues that face pathologists in the interpretation of adenomatous polyps are inaccurate sampling, recognition of muscularis mucosa in invasive malignancy, and the phenomenon of epithelial misplacement/pseudoinvasion.

Inaccurate Sampling

If the polyp is incompletely removed, the biopsy may not reveal the entire story because superficial biopsy may not include the muscularis mucosa or, as is often the case, the biopsy hits the benign part of the polyp and the malignant component is not included; therefore, the pathologist will give the report as benign and the authors think this is inappropriate. The authors have investigated this area[39] and showed that there was a false-negative report of 18.5% of MCRP when the original biopsies were compared with the subsequently completely resected specimens. The authors have since started using a template polyp report as follows: this is a tubular (or tubulovilous, or villous) neoplasm showing low-grade dysplasia (or high-grade dysplasia). If this is representative of the lesion then this is an adenoma; however, if this is part of a larger lesion then a more sinister pathology cannot be excluded. The authors feel that they have been honest with the clinician and the patient. Subsequently a Spanish group[40] showed a 18.8% false-negative pathology report on incompletely removed rectal polyps. Furthermore, the same study showed that 30.7% of the cohort were, in fact, T2 and 17.3% were T3, while the original biopsy was reported as benign.

Table 1: Risk factors for residual disease and suggested management plans in patients with malignant colorectal polyps.

Scoring the risk of residual disease in MCRP		
Histological data	**Degree of risk**	**Recommendation**
Resection margin <1 mm	++++	
Resection margin 1–2 mm	+	
Haggitt 4	++++	
Kikuchi 2	++	
Kikuchi 3	++++	
Poor differentiation	+++	
Mucinous tumour	+	
Tumour budding	+	
Lymphovascular invasion	++	
Score 0	Very low, <3%	Follow-up
Score +	Low, <5%	Assess other factors, careful follow-up
Score ++	Medium, 5–10%	Discuss risk and benefit of surgery
Score +++	High, 8–15%	Discuss risk with patients, more focus on surgery
Score ++++	Very high, >20%	Recommend surgery

MCRP: malignant colorectal polyps.

Adapted from Williams et al.[22]

Reporting proforma for colorectal carcinoma local excision specimens

Surname: …… Forenames: …… Date of birth: …… Sex: …..

Hospital…… Hospital no: …… NHS no: ……

Date of surgery: …… Date of report authorisation: …… Report no: ……

Date of receipt:…… Pathologist: …… Surgeon: ……

Specimen type†:

Polypectomy ☐ / Endoscopic mucosal resection (EMR) ☐ / Endoscopic submucosal dissection (ESD) ☐
Transanal endoscopic microsurgical (TEMS) excision ☐ / Other……

Site of tumour†:

Caecum ☐ / Right (ascending) colon ☐ / Hepatic flexure ☐ / Transverse colon ☐ / Splenic flexure ☐ /
Left (descending) colon ☐ / Sigmoid ☐ / Rectosigmoid ☐ / Rectum ☐ / Unknown ☐ / Tumour not identified ☐

Size of specimen (maximum width): .....mm Not assessable (piecemeal) ☐

Comments:……

Tumour type†:
Adenocarcinoma ☐ Other, or adenocarcinoma variant ☐
If Other, or variant, specify……

Differentiation by worst area†:
Well/moderate ☐ Poor ☐ Not applicable ☐

Local invasion:

No carcinoma identified (pT0)	☐
Submucosa (pT1)	☐
Muscularis propria (pT2)	☐
Beyond muscularis propria (pT3)	☐

For pT1 tumours only:
Maximum depth of invasive tumour from muscularis mucosae …… mm
Width of invasive tumour …… mm

For polypoid tumours only, Haggitt level:
1 ☐ / 2 ☐ / 3☐ / 4 ☐ /
Not applicable ☐ / Not assessable ☐

For sessile tumours only, Kikuchi level:
sm1 ☐ / sm2 ☐ / sm3 ☐/
Not applicable ☐ / Not assessable ☐

Number of lymph nodes†:……

Number of involved lymph nodes†:……

Number of tumour deposits: 0☐ 1☐ 2☐ 3☐ 4☐ 5☐ >5☐
Not applicable (if node positive) ☐

Deepest level of venous invasion:
None ☐ / Intramural☐ / Extramural ☐

Deepest level of lymphatic (small vessel) invasion:
None ☐ / Intramural☐ / Extramural ☐

Deepest level of perineural invasion:
None ☐ / Intramural☐ / Extramural ☐

Preoperative therapy response† (tumour regression score):

Not applicable	☐
No viable cancer cells (TRS 0)	☐
Single cells or rare small groups of cancer cells (TRS 1)	☐
Residual cancer with evident tumour regression (TRS 2)	☐
No evident tumour regression (TRS 3)	☐

Background adenoma: Yes ☐ No ☐

Involvement of margins by carcinoma†:

	Yes	No	Not assessable*
Peripheral margin	☐	☐	☐
Deep margin	☐	☐	☐

(*Not assessable is appropriate if specimen received piecemeal)
Histological measurement from carcinoma to nearest deep excision margin …… mm
Not assessable ☐

Pathological staging:
Complete resection of carcinoma (by >1mm) at all margins†:
Yes (R0)☐ No (R1)☐ No (R2)☐ Not assessable ☐

Figure 2: The RCPath dataset for reporting of local colorectal cancer excision specimens.[13]

The Recognition of Muscularis Mucosa in Invasive Malignancy

The issue of invasion beyond the muscularis mucosa is crucial, but characteristically the invading neoplastic cells secrete metaloprotein 9, which has been shown to destroy the muscularis mucosa.[41] Subsequently, Haboubi and Farroha[42] reported that when applying strict histological criteria, such as desmoplasia, irregularity of glands, high mitotic activity, tumour necrosis, and brisk inflammatory cell infiltrate, an experienced histopathologist can accurately diagnose cancer in the absence of muscularis mucosa, even from superficial biopsies.

Most literature and guidelines suggest that the presence of a desmoplastic stromal reaction to dysplastic glands is often considered acceptable for a diagnosis of invasive malignancy, as this phenomenon is rare in 'intramucosal adenocarcinoma'.[3,13] However, in biopsies taken from polypoid lesions, caution should be exercised as these can occasionally show desmoplastic stroma without the presence of submucosal invasion due to the effect of the previous endoscopic biopsies or partial polypectomy from the same site.[13]

A retrospective study for detection of desmoplastic reaction in biopsy specimens of early colorectal cancer from 359 patients with resected submucosal invasive colorectal cancers, who had undergone surgical or endoscopic mucosal resection, were analysed. For pedunculated, resected, submucosal, invasive colorectal cancers, the prevalence of desmoplastic reaction was not significantly related to submucosal depth. However, for non-pedunculated cancers, the prevalence of desmoplastic reaction in pre-treatment biopsy specimens was significantly related to submucosal depth.[43] In addition, the desmoplastic reaction positivity rate in pretreatment biopsy was significantly higher in those with a submucosal depth of ≥1,000 µm than those with a submucosal depth of <1,000 µm.

Epithelial Misplacement/ Pseudoinvasion

Epithelial misplacement, first described by Muto et al.[45] in 1973, refers to the misplacement of the mucosa into the submucosa that mimics invasive cancer and, in many cases, leads to diagnostic difficulty for pathologists. Even for experienced gastrointestinal pathologists, this phenomenon poses diagnostic difficulty in differentiating invasive carcinoma from pseudoinvasion.[21,44-46] It is commonly seen in prolapsed polyps in the sigmoid colon and is perceived to be one of the most difficult areas in the interpretation of polyps and in the context of a bowel cancer screening programme.

With the introduction of bowel cancer screening in many countries, there has been an improvement in the detection of early-stage cancer (e.g., Dukes A) in screened versus nonscreened populations (45.3% versus 10.1%, respectively).[2] In addition, adenomas are the most common type of polyp found during bowel cancer screening, comprising >60% of all polyps detected in the UK,[46] with the sigmoid adenomas being larger than similar polyps detected elsewhere in the bowel, and many of these tend to tort, bleed, and ulcerate. Despite this being a common and well-recognised phenomenon, this is still perceived as the most difficult area in the interpretation of polyps in the context of bowel cancer screening.[47-49] Recognising this difficult area, the British bowel cancer screening programme has created the 'Expert Board' in the UK, financed by the British programme, to deal with these difficult cases, and case referral is free. Since its establishment in 2009, >200 cases have been assessed by this board, which consists of three gastrointestinal pathologists to ensure a majority diagnosis, since agreement is by no means universal, emphasising the difficulty of this process. A recent paper describing difficult cases referred to the bowel cancer screening programme Expert Board showed that around 78.9% of the polyps referred were from the rectosigmoid junction and in 50% of cases the diagnosis was reversed from the opinion of the original reporting pathologist, in which the main issues were around epithelial misplacement.[49]

The main histological features that favour epithelial misplacement are:[21]

- The displaced epithelial is usually similar to that of the surface adenomatous component.
- Haemosiderin deposition.
- The presence of lamina propria around misplaced glands.

- Mucosal prolapse changes often present.
- Absence of budding, desmoplastic reaction, and lymphovascular invasion.

The bowel cancer screening programme recommends that all MCRP (part 1 polyp cancer) are to be reported by two pathologists with experience in gastrointestinal pathology to prevent overtreatment and unnecessary resections.[12,13] For consistency of reporting important data in a MCRP, the RCPath dataset is represented in Figure 2.

Currently, the options to treat a MCRP are local excision or major surgical excision, while some institutions adopt a 'wait and see' protocol. Major resection includes removal of lymph nodes, which provides therapeutic and staging benefits by identifying patients that may benefit from receiving adjuvant therapy.

CONCLUSION

The introduction of bowel cancer screening around the world has created unique difficulties in the interpretation of polyps, with epithelial misplacement being one of the most difficult areas. The authors propose that the histopathology report should include the grade of the tumour, completeness of excision, depth of invasion in millimetres, different staging systems whenever possible, and the presence of budding with lymphatic and vascular invasion. Once all these data become available, discussion of the report among the multidisciplinary management team is strongly recommended. The Association of Coloproctology of Great Britain and Ireland (ACPGBI) prepared a position statement,[22] with questions to consider should the endoscopist be faced with a suspected MCRP: 'Can the lesion be removed endoscopically?', and 'Should it be removed endoscopically?', 'Can I remove it endoscopically?', 'Can I remove it in one session?'. The position statement also attempted to draw together the risk factors into a global assessment of risk of residual disease and suggested a course of action to be discussed with the patient in a chart that can be modified as more data are collected (Table 1).

References

1. Quirke P et al.; International Agency for Research on Cancer. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition–Quality assurance in pathology in colorectal cancer screening and diagnosis. Endoscopy. 2012;44(Suppl 3): SE116-30.
2. Mohamed M, Schofield JB. The pathology of colorectal polyps and cancers (including biopsy). Surgery (Oxford). 2014;32(4):165-71.
3. Logan RF et al.; English Bowel Cancer Screening Evaluation Committee. Outcomes of the Bowel Cancer Screening Programme (BCSP) in England after the first 1 million tests. Gut. 2012;61(10):1439-46.
4. Ellul P et al. Downstaging of colorectal cancer by the national bowel cancer screening programme in England: First round data from the first centre. Colorectal Disease. 2010;12(5):420-2.
5. Williams AR et al. Polyps and cancer of the large bowel: A necropsy study in Liverpool. Gut. 1982;23(10):835-42.
6. Bujanda L et al. Malignant colorectal polyps. World J Gastroenterol. 2010;16(25):3103-11.
7. Stryker SJ et al. Natural history of untreated colonic polyps. Gastroenterology. 1987;93(5):1009-13.
8. Bosman FT, "WHO classification of tumours of the digestive system," Bosman FT et al. (eds.), World Health Organization classification of tumours 2010, 4th edition, Lyon: IARC Press.
9. Nusko G et al. Risk of invasive carcinoma in colorectal adenomas assessed by size and site. Int J Colorectal Dis. 1997;12(5):267-71.
10. Lieberman D et al. Polyp size and advanced histology in patients undergoing colonoscopy screening: Implications for CT colonography. Gastroenterology. 2008;135(4):1100-5.
11. Levene Y et al. The correlation between endoscopic and histopathological measurements in colorectal polyps. Histopathology. 2015;66(4):485-90.
12. Public Health England. NHS Bowel Cancer Screening Programme: Guidance on reporting lesions. 2018. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/694063/bowel_cancer_screening_programme_guidance_on_reporting_lesions.pdf. Last accessed: 2 October 2018.
13. Loughrey MB et al.; The Royal College of Pathologists. Standards and datasets for reporting cancers: Dataset for histopathological reporting of colorectal cancer. 2018. Available at: https://www.rcpath.org/resourceLibrary/g049-dataset-for-histopathological-reporting-of-colorectal-cancer.html. Last accessed: 2 October 2018.
14. Riddell RH et al. Dysplasia in inflammatory bowel disease: Standardized classification with provisional clinical applications. Hum Pathol. 1983;14(11):931-68.
15. Dixon MF. Gastrointestinal epithelial neoplasia: Vienna revisited. Gut. 2002;51(1):130-1.
16. Osmond A et al. Interobserver variability in assessing dysplasia and architecture in colorectal adenomas: A multicentre Canadian study. J Clin Pathol. 2014;67(9):781-6.
17. Foss FA et al. Pathology of polyps detected in the bowel cancer screening programme. Diagnostic Histopathology. 2011;17(11):495-504.
18. Lieberman DA et al. Guidelines for colonoscopy surveillance after screening and polypectomy: A consensus update by the US multi-society task force on

colorectal cancer. Gastroenterology. 2012;143(3):844-57.

19. Duff SE et al. Lymphatic vessel density, microvessel density and lymphangiogenic growth factor expression in colorectal cancer. Colorectal Dis. 2007;9(9):793-800.
20. The Paris endoscopic classification of superficial neoplastic lesions: Esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc. 2003;58(6 Suppl):S3-43.
21. Loughrey MB, Shepherd NA. Problematic colorectal polyps: Is it cancer and what do I need to do about it? Surg Pathol Clin. 2017;10(4):947-60.
22. Williams JG al.; Association of Coloproctology of Great Britain and Ireland. Management of the malignant colorectal polyp: ACPGBI position statement. Colorectal Dis. 2013;15 Suppl 2:1-38.
23. Hassan C et al. Histologic risk factors and clinical outcome in colorectal malignant polyp: A pooled-data analysis. Dis Colon Rectum. 2005;48(8):1588-96.
24. Lugli A et al. Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016. Mod Pathol. 2017;30(9):1299-311.
25. Lee SJ et al. The significance of tumor budding in T1 colorectal carcinoma: The most reliable predictor of lymph node metastasis especially in endoscopically resected T1 colorectal carcinoma. Hum Pathol. 2018;78:8-17.
26. Beaton C et al. Systematic review and meta-analysis of histopathological factors influencing the risk of lymph node metastasis in early colorectal cancer. Colorectal Dis. 2013;15(7): 788-97.
27. Kikuchi R et al. Management of early invasive colorectal cancer. Risk of recurrence and clinical guidelines. Dis Colon Rectum. 1995;38(12):1286-95.
28. Haggitt RC et al. Prognostic factors in colorectal carcinomas arising in adenomas: Implications for lesions removed by endoscopic polypectomy. Gastroenterology. 1985;89(2):328-36.
29. Edge SB, Compton CC. The American Joint Committee on Cancer: The 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17(6):1471-4.
30. Lopez A et al. Outcomes following polypectomy for malignant colorectal polyps are similar to those following surgery in the general population. Gut. 2017. [Epub ahead of print].
31. Fischer J et al. Management of malignant colorectal polyps in New Zealand. ANZ J Surg. 2017;87(5): 350-5.
32. Kudo S. Endoscopic mucosal resection of flat and depressed types of early colorectal cancer. Endoscopy. 1993;25(7):455-61.
33. Ueno H et al. Risk factors for an adverse outcome in early invasive colorectal carcinoma. Gastroenterology. 2004;127(2): 385-94.
34. Nascimbeni R et al. Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. Dis Colon Rectum. 2002;45(2):200-6.
35. Wang LM et al. Ueno method substaging pT1 colorectal adenocarcinoma by depth and width measurement: An inter-observer study. Colorectal Dis. 2015;17(8): 674-81.
36. Davenport A et al. Interobserver variability amongst gastrointestinal pathologists in assessing prognostic parameters of malignant colorectal polyps: A cause for concern. Tech Coloproectol. 2016;20(9):647-52.
37. Komuta K et al. Interobserver variability in the pathological assessment of malignant colorectal polyps. Br J Surg. 2004;91(11): 1479-84.
38. Balyasnikova S et al. Histopathological and radiological reporting in rectal cancer: Concepts and controversies, facts and fantasies. Tech Coloproctol. 2017;21(1):15-23.
39. Absar MS, Haboubi NY. Colonic neoplastic polyps: Biopsy is not efficient to exclude malignancy. The Trafford experience. Tech Coloproctol. 2004;8 Suppl 2:s257-60.
40. Serra-Aracil X et al. Transanal endoscopic surgery with total wall excision is required with rectal adenomas due to the high frequency of adenocarcinoma. Dis Colon Rectum. 2014;57(7):823-9.
41. Jeziorska M et al. Distribution of gelatinase B (MMP-9) and type IV collagen in colorectal carcinoma. Int J Colorectal Dis. 1994;9(3):141-8.
42. Haboubi N, Farroha M. Experienced histopathologists can accurately diagnose colorectal carcinoma (CRC) in the absence of Muscularis mucosa (MM). Colorectal Disease. 2013;15(Suppl 3):78.
43. Hirose M et al. Detection of desmoplastic reaction in biopsy specimens is useful for predicting the depth of invasion of early colorectal cancer: A Japanese collaborative study. J Gastroenterol. 2010;45(12):1212-8.
44. Cooper HS et al. Endoscopically removed malignant colorectal polyps: Clinicopathologic correlations. Gastroenterology. 1995;108(6): 1657-65.
45. Muto T et al. Pseudo-carcinomatous invasion in adenomatous polyps of the colon and rectum. J Clin Pathol. 1973;26(1):25-31.
46. Loughrey MB, Shepherd NA. The pathology of bowel cancer screening. Histopathology. 2015;66(1):66-77.
47. Shepherd NA, Griggs RK. Bowel cancer screening-generated diagnostic conundrum of the century: Pseudoinvasion in sigmoid colonic polyps. Mod Pathol. 2015; 28 Suppl 1:S88-94.
48. Bowel Cancer Screening Programme Pathology Group. Reporting lesions in the NHS Bowel Cancer Screening Programme. 2007. Available at: http://www.bcsp.nhs.uk/files/NHS%20BCSP%20Publication%201.pdf. Last accessed: 2 October 2018.
49. Griggs RK et al. Challenging diagnostic issues in adenomatous polyps with epithelial misplacement in bowel cancer screening: 5 years' experience of the Bowel Cancer Screening Programme Expert Board. Histopathology. 2017;70(3):466-72.

Non-Cardiac Chest Pain: A Review of Environmental Exposure-Associated Comorbidities and Biomarkers

Authors: Mena Mikhail,[1] George Crowley,[1] Syed Hissam Haider,[1] Arul Veerappan,[1] Rachel Lam,[1] Angela Talusan,[1] Emily Clementi,[1] Dean Ostrofsky,[1] Sophia Kwon,[1] *Anna Nolan[1,2,3]

1. Department of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, New York University School of Medicine, New York City, New York, USA
2. Department of Environmental Medicine, New York University School of Medicine, New York City, New York, USA
3. Bureau of Health Services and Office of Medical Affairs, Fire Department of New York City, New York, USA

*Correspondence to anna.nolan@med.nyu.edu

Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: This research was funded by the National Heart, Lung, and Blood Institute (NHLBI R01HL119326) and the Center for Disease Control/National Institute for Occupational Safety and Health (CDC/NIOSH U01-OH011300). The funding agencies did not participate in the study design; collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication. All authors made substantial contributions to the study. The primary investigator was Dr Nolan. The study was designed by Dr Nolan, Dr Mikhail, Dr Crowley, and Dr Kwon. All authors participated in the writing and revision of the report and approval of the final version.

Received: 31.08.18

Accepted: 24.10.18

Keywords: Biomarkers, environmental exposure, gastro-oesophageal reflux, non-cardiac chest pain (NCCP), obstructive airway disease (OAD), particulate matter (PM).

Citation: EMJ Gastroenterol. 2018;7[1]:103-112.

Abstract

The prevalence of non-cardiac chest pain (NCCP) ranges from 13–33%. A majority of those presenting with a chief complaint of chest pain are found to have a diagnosis of NCCP. Aerodigestive diseases are a cause of NCCP, and billions of dollars are spent annually on the treatment of NCCP. Furthermore, NCCP can cause significant psychological stress. NCCP is commonly diagnosed when patients have chest pain despite a normal cardiac evaluation. The leading cause of NCCP is gastro-oesophageal reflux disease (GORD). GORD should be suspected in patients who report a history of acid regurgitation, cough, dysphagia, and bloating. Another common cause of NCCP is obstructive airway disease (OAD). A thorough history and review of the symptoms should be performed for those with suspected NCCP, especially because of the contributing end organs. It is known that environmental exposures can commonly cause GORD and OAD; however, NCCP has not been fully explored in the context of environmental exposure. Patients with a history of exposure to particulate matter can develop environmental-exposure-associated GORD and coexisting OAD. This narrative review aims to provide a practical overview of NCCP, its causes, their relation to environmental exposure, and associated biomarkers. The authors used a PubMed search that spanned 2003–2018 to accomplish this. Additionally, this review provides

a broad overview of biomarkers of GORD-associated NCCP and OAD-associated NCCP due to environmental exposure.

INTRODUCTION

Chest pain (CP) accounts for 5.7% of emergency department (ED) visits in the USA each year.[1] The differential of CP is broad and often includes acute coronary syndrome, which requires a costly work-up and may lead to inpatient care; however, in one study,[2] 57% of patients presenting with CP were found to have non-cardiac CP (NCCP). The prevalence of NCCP ranges from 13–33% in subjects complaining of CP.[3-6]

The treatment of NCCP is a global health concern. In a cohort study of USA veterans, the cost of care of CP patients with a low pretest probability for coronary artery disease was $57,336 per patient.[7] Another study showed that the high ratio of NCCP cases to cardiac CP (CCP) cases may cause the cumulative annual cost of NCCP to exceed that of CCP.[8] Sick leave and interruptions in work-related activities have been seen in 30–60% of patients with NCCP.[9] A recent study found that $13 billion were spent annually on CP treatment, and 50% of CP patients were found to have no evidence of cardiac disease.[10]

NCCP was defined as recurring CP that cannot be differentiated from CCP and has a negative evaluation for cardiac causes.[11] Differentiating acute coronary syndrome from NCCP involves the assessment of serum levels of cardiac biomarkers, such as troponin and creatinine-kinase-muscle brain levels; electrocardiography; chest X-ray; and lipid profile.[12]

Studies have shown that the most common cause of NCCP is gastro-oesophageal reflux disease (GORD). In a 2007 study of 78 patients with NCCP, the prevalence of GORD was 44.8%.[13] Additionally, of the 35 patients who had GORD-induced NCCP, 57.1% and 48.6% reported heartburn (HB) and regurgitation, respectively.[13] Another cause of NCCP is obstructive airway disease (OAD), with nearly half of patients with OAD reporting CP.[14] In addition to OAD and GORD, anxiety has been studied as a contributor to NCCP, with NCCP patients exhibiting higher State Trait Anxiety Inventory scores than controls in a 2014 study.[15]

OAD and GORD are prevalent in those with a history of occupational or environmental exposure.[16-20] In firefighters with World Trade Center (WTC) particulate matter (PM) exposure, there was a significant increase in the prevalence of GORD from 38.4% to 43.8% in the cohort 4 years after the 11th September 2001 terrorist attack at the WTC (9/11).[21] Additionally, the biomarker profile of patients with GORD and OAD secondary to PM exposure has been explored by our group and others and may provide insight into contributing pathways.[22-40]

This review presents an overview of NCCP, its unique features with respect to CCP, the causative role of environmental exposures, and the biomarkers of GORD and OAD, two conditions caused by environmental exposure that can lead to NCCP.

METHODS

Search Strategy

PubMed databases were searched on 28th June 2018. The search was limited to articles that were published within the last 15 years, from 1st January 2003–28th June 2018. Cohort studies, case control studies, narrative reviews, meta-analyses, and statistical summaries were retrieved. Titles, abstracts, and full texts were screened based on relevance to this review. Keywords searched included 'non-cardiac chest pain', 'gastroesophageal reflux disease', 'obstructive airway disease', 'air pollution', 'particulate matter', 'occupational exposure', 'World Trade Center', 'chronic obstructive pulmonary disease', 'chest pain', 'predictive biomarkers', 'low risk chest pain', 'HEART Score', and 'emergency department summary'. Furthermore, the references of many of the articles identified by the above search strategy were reviewed.

Inclusion and Exclusion Criteria

Studies were included in this narrative review if they were observational, retrospective,

systematic reviews, or clinical studies; focussed on providing the epidemiology and aetiology of NCCP; assessed the relation of NCCP with OAD and GORD; discussed OAD and GORD in the context of environmental exposure; or focussed on the use of biomarkers to evaluate environmental-associated causes of NCCP. Studies were excluded if they were published earlier than 2003, were not written in English, or were not conducted on human subjects. Studies that were included in this review were available in their entirety online and were referenced using EndNote® X7 (Thomson Reuters, Philadelphia, Pennsylvania, USA).

RESULTS AND DISCUSSION

Differentiating Non-Cardiac Chest Pain from Cardiac Chest Pain

Several recent studies have attempted to identify low-cost methods of differentiating NCCP and CCP. In a cohort of 331 patients who experienced an acute myocardial infarction, 90% of those reported CP >20 minutes in duration.[41] CCP is located proximally, while NCCP localises to the middle-left side of the chest. The same study found that patients with NCCP took medications for CP relief at a lower rate than their CCP counterparts.[42]

Decision-Making Tools and Scoring Systems That Have Recently Been Used to Risk-Stratify Chest Pain Patients

The HEART Score uses history, ECG findings, age, risk factors, and troponin levels to risk-stratify patients, and has been shown to be able to be used to safely discharge low-risk CP patients from the ED at a higher rate than clinician judgement alone.[43] In a 2017 prospective cohort study, use of the HEART pathway, which incorporated the HEART score, resulted in $904,952 in-hospital costs saved over 1 year.[44] The North American Chest Pain Rule (NACPR) considers new ischaemic ECG changes, a history of coronary artery disease, the Diamond-Forrester Classification, and troponin levels >99th percentile. If a patient does not meet any of these four criteria, then additional diagnostic studies are not necessary and the patient can be discharged from the ED. In a 2017 cohort study,[45] none of those classified by NACPR as very low risk experienced complications 30 days after discharge.

Recent Serum Biomarkers for Differentiating Types of Chest Pain

Along with clinical decision-making tools, serum biomarkers have also been used in the stratification of CP patients. A 2017 study demonstrated that 97% of a subset of low-risk CP patients with normal levels of cystatin C and N-terminal pro-B type natriuretic peptide had normal stress ECG.[46] Further studies assessing the effectiveness of using these biomarkers in low-risk CP patients are warranted.

Differential Diagnosis of Non-Cardiac Chest Pain

NCCP has a broad differential, including pulmonary, gastrointestinal, and musculoskeletal causes (Figure 1). The authors will focus on two of the most common causes of environment-associated NCCP: GORD and OAD, highlighted yellow in Figure 1. GORD is the main contributing factor in up to 50% of patients with CP.[47] Multiple studies have supported GORD's association with NCCP.[48-51] GORD is also often found in OAD patients.[52]

Gastro-Oesophageal Reflux Disease as a Cause of Non-Cardiac Chest Pain

The underlying mechanism of GORD-related NCCP is still an area of active investigation. Oesophageal distension and hypersensitivity have been identified as possible aetiologies. In one case-control study,[53] ultrasound imaging demonstrated that patients undergoing a GORD episode had higher cross-sectional area of the oesophagus than controls. Oesophageal hypersensitivity as a cause of NCCP has also been postulated; acid infusion in the distal oesophagus resulted in the lowering of the oesophageal pain threshold in both NCCP and healthy patients.[54] Reflux episode duration and acid clearance have been shown to contribute to NCCP.[55] A 24-hour ambulatory pH assessment was used to monitor reflux episodes in 120 subjects. Those who reported CP experienced both longer reflux episodes and acid clearance times.[55]

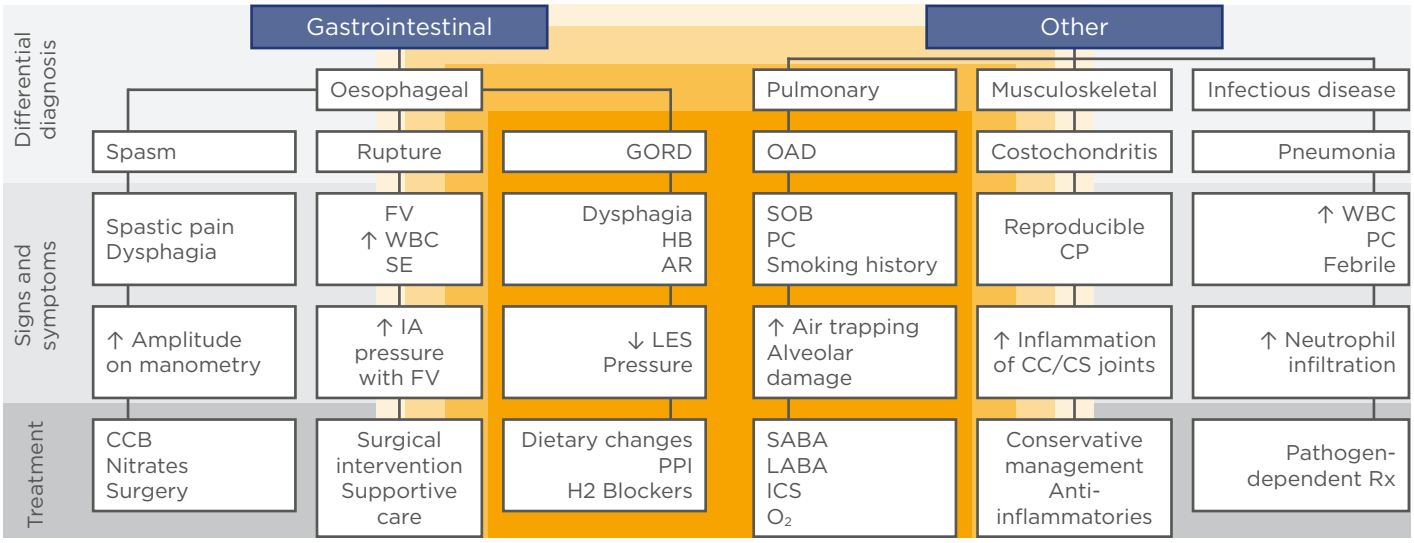


Figure 1: Overview of the differential diagnosis and treatment of chest pain.

PM-associated conditions highlighted in yellow.

↑: increased; ↓: decreased; AR: acid regurgitation; CC: costochondral; CCB: calcium channel blocker; CP: chest pain; CS: costosternal; FV: forceful vomiting; GORD: gastro-oesophageal reflux disease; H2: histamine receptor 2; HB: heartburn; IA: intra-abdominal; ICS: inhaled corticosteroids; LABA: long-acting beta-agonist; LES: lower oesophageal sphincter; OAD: obstructive airway disease; PC: productive cough; PPI: proton pump inhibitor; Rx: treatment; SABA: short-acting beta-agonist; SOB: shortness of breath; SE: subcutaneous emphysema; WBC: white blood cells.

Gastro-Oesophageal Reflux Disease due to Environmental Exposure

Although there are established risk factors, such as socioeconomic status, obesity, and cigarette smoking, that contribute to the pathogenesis of GORD,[56,57] the effect of PM exposure remains an important topic. Studies of environmental exposure and GORD have identified a positive association between the two. In a longitudinal study of Fire Department of New York (FDNY) firefighters, it was determined that GORD was the condition with the highest incidence after 9/11, followed by OAD and chronic rhinosinusitis.[16] It was suggested that aerodigestive tract inflammation contributed to the development of GORD.[16] In a 2011 retrospective study of WTC-PM-exposed subjects, the incidence of symptoms related to GORD after 9/11 was 20.3%. Two-thirds of those affected still had persistent symptoms up to at least 6 years after the attacks.[17]

A 2015 clinical study[18] showed that patients who had a history of inhalational injury due to sulfur mustard exposure had higher frequencies of GORD symptoms than controls. In a sample size of 120 patients who were exposed to sulfur mustard, acid regurgitation and HB were reported at frequencies of 40.8% and 51.7%, respectively; this was a significantly higher percentage than the control group, in which 6.7% and 8.8% of participants were affected by acid regurgitation and HB, respectively. A study reported that, out of 1,650 subjects who completed an occupational exposure survey, the subset of 224 subjects further classified with a complication of GORD known as Barret's oesophagus (BO), reported higher self-reported asbestos exposure frequencies than the controls.[58]

Obstructive Airway Disease as a Cause of Non-Cardiac Chest Pain

There are several potential mechanisms that contribute to OAD patients experiencing thoracic pain. The activation of the visceral pleura receptors has been implicated. Hyperinflation of the lungs seen in chronic obstructive pulmonary disease (COPD) patients causes the visceral pleura to stretch and, as a result, activate the

visceral pleura receptors that are connected to the pulmonary parenchyma, leading to pain.[59] The intercostal nerves that transmit nociceptive information through the intercostal nerves to the central nervous system have also been suggested as a cause of chronic CP in COPD patients.[59] In a 2016 cross-sectional observational study,[60] 67 patients with OAD were interviewed about the severity and location of their pain, and underwent spirometry and plethysmography. Thoracic pain was reported in 53.7%, in either an isolated pattern or accompanied with pain in another area. Despite the high prevalence of thoracic pain in this study, there were no significant correlations between thoracic pain, hyperinflation, and pulmonary function test data.

Obstructive Airway Disease and Environmental Exposure

In a cross-sectional study conducted in 2017,[19] seven district clusters were randomly selected from four Chinese cities with different pollution levels. PM concentrations for each cluster were measured and subjects underwent spirometry. From the data, it was suggested that subjects from areas that had higher concentrations of PM were more prone to obstructive symptoms such as cough, dyspnoea, and wheezing; however, in this study, the effect of PM on COPD was not statistically significant in non-smokers.

In WTC-PM-exposed FDNY rescue workers referred for pulmonary evaluation, 59% of the cohort had indications of OAD, such as elevated residual volume, airway hyper-reactivity, and bronchodilator responsiveness.[40] In a 2010 cohort study, significant declines in forced expiratory volume in 1 second (FEV_1) were seen in a cohort of firefighters and emergency medical service workers who responded to the WTC terrorist attacks.[61] The incidence of those with FEV_1 less than the lower limit of normal (LLN) increased in the 6 years after 9/11.[61]

In a longitudinal study that spanned 20 years, 3,343 people between the ages of 20 and 44 years underwent a detailed questionnaire, spirometry, and occupational assessment. Subjects with COPD or asthma at baseline were excluded. Subjects provided details regarding their occupation and their responses were coded by the International Standard Classification of Occupations (ISCO). These codes were then linked to the ALOHA Job-Exposure Matrix that assigned grades of no, low, or high exposure to various agents for every job code. It was demonstrated that those who were exposed to toxins had a higher incidence of COPD.[20]

The pathophysiologic and cellular response contributions of PM-exposure to OAD are under investigation. In a systematic review, it was argued that a wide array of proteins that signal a downstream effect of inflammation and oxidative stress can contribute to the pathogenesis of OAD secondary to PM exposure.[62] PM exposure of alveolar macrophages and pulmonary epithelial cells led to the release of proinflammatory mediators, such as granulocyte-monocyte colony stimulating factor (GM-CSF), TNF-α, IL-1, IL-8, and IL-6, that facilitate the recruitment of neutrophils and other leukocytes to mediate lung tissue damage.[63]

Serum Biomarkers of Particulate Matter-Associated Morbidity and Associated Non-Cardiac Chest Pain Conditions

Studies concerning the use of serum biomarkers to assist in the diagnosis, monitoring, and understanding of PM-associated GORD and OAD pathogenesis have been conducted (Table 1).[22-27,29-31,33,35-39,64,65]

Known for its pathophysiologic contributions to cancer, metabolic syndrome, and other conditions, the soluble receptor for advanced glycation end-products has been highly associated with cases of WTC lung injury (WTC-LI), defined as percent FEV_1 of predicted normal (FEV_1%Pred) <LLN, relative to controls.[22] Macrophage-derived chemokine and GM-CSF have been associated with a FEV_1%Pred<LLN in firefighters exposed to WTC-PM.[23] Metabolic biomarkers, such as glucose, triglycerides, and lipoproteins, can be used to assess pulmonary function loss. In a 2012 nested case control study,[39] elevated glucose and leptin levels were predictive of the development of WTC-LI. In cases of WTC-LI, there was also a higher prevalence of individuals with characteristics of metabolic syndrome.[39] It has been demonstrated that certain biomarkers could exert a protective effect against OAD.

Table 1: Biomarkers of non-cardiac chest pain due to environmental exposure.

Study	Country	Population/design/exposure	Study size	Compartment/ assay	End points	Classification	Significant findings
Haider et al.,[64] 2018	USA	FDNY WTC-PM exposed firefighters. A case-control study.	285	C-peptide TNF-α IP-10 Fractalkine	GORD/ BO	Polypeptide Cytokine Cytokine Chemokine	GORD and BO cases had similar lung function, D_{LCO}, bronchodilator response, and long-acting β-agonist use compared to controls. In confounder-adjusted regression models, TNF-α ≥6 pg/mL predicted both GORD and BO. GORD was also predicted by C-peptide ≥360 pg/mL, while BO was predicted by fractalkine ≥250 pg/mL and IP-10 ≥290 pg/mL. Finally, participants with GORD had significantly increased use of short-acting β-agonist compared to controls.
Caraher et al.,[22] 2017	USA	WTC-PM exposed firefighters. sRAGE in pulmonary decline in this group was studied in a case-cohort study.	185	sRAGE CRP MMP-9	OAD	Receptor Acute phase Enzyme	Odds of developing WTC-LI increased additionally by 1.2, 1.8, and 1.0 in firefighters with sRAGE ≥97pg/mL, CRP ≥2.4mg/L, and MMP-9 ≤397ng/mL, respectively, assessed in a multivariate logistic regression model (AUC of 0.72).
Nolan et al.,[23] 2012	USA	WTC-PM exposed firefighters. A case-cohort study.	194	MDC GM-CSF	OAD	Cytokines	Elevations in MDC and GM-CSF increased risk of FEV_1<LLN by 3.0-fold and 2.5-fold, respectively.
Hoffman et al.,[24] 2009	Germany	45–75-year-olds with PM exposure in industrialised areas in a prospective cohort study.	4,032	CRP Fibrinogen	OAD	Acute phase	PM exposure was associated with a 23.9% and 3.9% increase in CRP and fibrinogen, respectively, in males.
Nazariah et al.,[25] 2013	Malaysia	Malaysian children subjected to indoor PM. Obstructive airway symptoms and IL-6 concentrations were assessed in a case–control study.	430	IL-6	OAD	IL	Higher PM exposure in urban setting strongly associated with elevated IL-6 sputum concentrations, and had higher prevalence of respiratory symptoms.
Dadvand et al.,[26] 2014	Spain	COPD patients exposed to PM and NO_2. A cross-sectional study.	242	CRP Fibrinogen HGF	OAD	Acute phase Growth factor	Positive correlation between the three biomarkers and NO_2 exposure, but not PM2.5.
Canova et al.,[27] 2012	UK	Population with pre-existing asthma or COPD with PM exposure. A case-cross over study.	209	GSTP-1 SOD-2 Nrf2	OAD	Genotypes	All three genetic polymorphisms were associated with increased risk of COPD and asthma exacerbation with 10 ug/m3 increase of PM10.
Kwon et al.,[36] 2013	USA	Rescue and recovery workers. Exposed to WTC-PM. A nested case control study.	193	MMP-3 MMP-12	OAD	Enzymes	Each log-increase in MMP-3 and MMP-12 showed reduced odds of developing WTC-LI by 73% and 54%, respectively. MMP-3 and MMP-12 consistently clustered together in cases, controls, and the cohort. Increasing time to blood draw significantly and independently increased the risk of WTC-LI.
Naveed et al.,[39] 2012	USA	Nested case control study of FDNY rescue workers exposed to WTC-PM.	237	HDL Glucose Triglycerides Leptin Amylin	OAD	Lipoprotein Simple sugar Lipid Hormone	Cases and control subjects had significant differences in HDL <40 mg/dL with triglycerides ≥150 mg/dL, heart rate ≥66 bpm, and leptin ≥10,300 pg/mL. Each increased the odds of abnormal FEV_1 at pulmonary evaluation by more than 2-fold, whereas amylin ≥116 pg/mL decreased the odds by 84%, in a multibiomarker model adjusting for age, race, BMI, and WTC arrival time. The model had a sensitivity of 41%, a specificity of 86%, and an AUC of 0.77.
Nolan et al.,[30] 2014	USA	Firefighters exposed to WTC-PM. A nested case control study.	188	MMP-2 TIMP-1	OAD	Enzyme Protease inhibitor	FEV_1 in cases and controls declined 10% of after 9/11. Cases subsequently returned to 99% of their pre-exposure FEV_1 while decline persisted in controls. Elevated TIMP-1 and MMP-2 increased the odds of resistance by 5.4 and 4.2-fold, respectively, while elevated MMP-1 decreased it by 0.27-fold.
Lee et al.,[29] 2015	Taiwan	COPD and non-COPD subjects. Predictive biomarkers assessed in a cohort of subjects exposed to PM from air pollution in a prospective cohort study.	65	ITIH-4	OAD	Protease inhibitor	Decreased levels of ITIH-4 correlated with PM exposure with COPD patients.

Table 1 continued.

Study	Country	Population/design/exposure	Study size	Compartment/ assay	End points	Classification	Significant findings
Montano et al.,[31] 2014	Mexico	Population with a history of biomass and tobacco smoke exposure, and healthy patients. FEV_1 and metabolic profile analysed in a case control study.	120	MMP-1 MMP-7 MMP-9 TIMP-2 CRP	OAD	Enzymes Protease inhibitor Acute phase	Both combustion and tobacco exposure cohorts exhibited increased plasma levels of MMP-1, MMP-7, MMP-9, and CRP, and a steeper decline in FEV_1.
Weiden et al.,[38] 2013	USA	FDNY firefighters exposed to WTC-PM. Cardiovascular biomarkers assessed in a nested case cohort study.	258	Apo-AI Apo-AII Apo-CII Apo-CIII Apo-E MIP-4 sVCAM MPO	OAD	Lipoproteins Protease inhibitor Adhesion molecule Enzyme	Susceptible WTC-LI cases had higher levels of Apo-A2, CRP, and MIP-4 with significant relative risks of 3.85, 3.93, and 0.26, respectively, with an AUC of 0.858. Resistant WTC-LI cases had significantly higher sVCAM-1 and lower MPO, with relative risks of 2.24 and 2.89, respectively (AUC 0.830).
Tsukiji et al.,[35] 2014	USA	Firefighters with WTC-PM exposure. A nested case-control study.	173	LPA Apo-AI	OAD	Phospholipid Lipoprotein	LPA and Apo-A1 levels were higher in cases than controls and predictive of case status. LPA increased the odds by 13%, while Apo-A1 increased the odds by 29% of an FEV_1 <LLN in a multivariable model.
Singh et al.,[33] 2018	USA	FDNY firefighters that were exposed to WTC-PM. A longitudinal cohort study.	215	Eosinophils IL-4 IL-21 IFN-gamma	OAD	Leukocyte Cytokines	Eosinophil concentration ≥300 cells/µL was associated with increased risk of asthma/COPD overlap (HR: 1.85) but not with isolated-asthma or isolated-COPD. Serum IL-4 also predicted asthma/COPD overlap (HR: 1.51) per doubling of cytokine concentration. Greater IL-21 concentration was associated with both isolated-asthma and isolated-COPD (HR of 1.73 and 2.06, respectively).
Zeig-Owens et al.,[65] 2018	USA	Firefighters that were exposed to WTC-PM. Blood leukocytes evaluated in a cohort study.	9,434	Eosinophils Neutrophils	OAD	Leukocytes	Higher post-9/11 blood neutrophil and eosinophil concentrations were associated with subsequent accelerated FEV_1 decline in WTC-exposed firefighters. Both higher blood eosinophil concentrations and accelerated FEV_1 decline were associated with incident airflow limitation in WTC-exposed firefighters.
Cho et al.,[37] 2013	USA	WTC-PM exposed firefighters. Biomarkers of WTC-LI assessed in a nested case control study.	251	Chitotriosidase IgE	OAD	Enzyme Ig	Increased serum chitotriosidase reduces the odds of developing obstruction after WTC-PM exposure and is associated with recovery of lung function. Alternately, elevated IgE is a risk factor for airflow obstruction and progressive lung function decline.

Apo: apolipoprotein; AUC: area under the curve; BO: Barrett's oesophagus; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; D_{LCO}: diffusing capacity of the lung for carbon monoxide; FDNY: Fire Department of New York; FEV_1: forced expiratory volume in 1 second; GORD: gastro-oesophageal reflux disease; GM-CSF: granulocyte-monocyte colony stimulating factor; GSTP-1: glutathione S-transferase 1; HDL: high density lipoprotein; HGF: hepatocyte growth factor; HR: hazard ratio; IP-10: interferon-gamma inducing protein 10; ITIH-4: inter-alpha-trypsin inhibitor 4; LPA: lysophosphatidic acid; LLN: lower limit of normal; MDC: macrophage-derived chemokine; MIP-4: macrophage inflammatory protein-4; MMP: matrix metalloproteinase; MPO: myeloperoxidase; Nrf2: nuclear factor 2; OAD: obstructive airway disease; PM: particulate matter; SOD2: superoxide dismutase 2; sRAGE: soluble receptor for advanced glycation end-products; sVCAM: soluble vascular cell adhesion molecule-1; TIMP: tissue inhibitor of metalloproteinase; WTC-LI: World Trade Center lung injury; WTC-PM: World Trade Center particulate matter.

Elevated levels of matrix-metalloproteinase (MMP)-2 and tissue inhibitor of MMP-1, were associated with increased resistance to WTC-LI.[30] MMP-3 and MMP-12 were also found to exert a protective effect from developing WTC-LI in a cohort of FDNY firefighters.[36]

In a 2009 study,[24] PM exposure was associated with a 23.9% and 3.9% increase of C-reactive protein and fibrinogen, respectively, in a cohort of individuals from highly industrialised areas in Germany. In a 2013 study,[25] high PM exposure was not only associated with increased reporting of obstructive airway symptoms relative to low PM exposure but also was strongly associated with higher sputum IL-6 concentrations. In a cohort of 251 COPD patients, C-reactive protein, hepatocyte growth factor, and fibrinogen were strongly associated with nitrate dioxide exposure in a 2014 study conducted in Spain.[26] Genomic biomarkers have also been used to establish incidence of exposure. Glutathione S-transferase 1, superoxide dismutase 2, and nuclear factor 2 were associated with a slight risk for hospitalisation due to COPD and asthma exacerbation secondary to PM exposure.[27]

Decreased levels of inter-alpha-trypsin inhibitor-4 have been associated with PM exposure in a cohort of PM-exposed subjects in Taiwan.[29] Specifically, levels of inter-alpha-trypsin inhibitor-4 were significantly lower in patients with OAD than healthy subjects regardless of their smoking status, up to 3-years post exposure. Increased levels of MMP-1, 7, 9, and tissue inhibitor of MMP-1 were seen in a cohort of COPD patients with biomass exposure and were associated with a significantly lower FEV_1 relative to the controls and those with COPD secondary to tobacco smoke exposure.[31]

Biomarkers of Gastro-Oesophageal Reflux Disease

As with studies of OAD patients, serum biomarkers were also used to establish incidence of GORD secondary to PM exposure. In a 15-year longitudinal study published in 2018,[64] biomarkers were identified in a sub-cohort of WTC-PM-exposed FDNY firefighters. A sample of 265 FDNY rescue workers exhibited elevated levels of three serum biomarkers; TNF-α, C-peptide, and MMP-9 were found to be significant predictors of developing GORD secondary to PM exposure.

Expressions of claudin-1 and 2, zonula occludens-1, and filaggrin were found to be changed in those with GORD, as discussed in a 2016 systematic review.[66] The same review demonstrated that not only was proteinase-activated receptor-2 (PAR-2) overexpressed in GORD patients but PAR-2 also contributes to the pathogenesis of GORD in the context of visceral hypersensitivity.[65] It has been argued that the activation of PAR-2 gives rise to the release of IL-8, causing inflammatory changes and subsequent GORD.[67]

Biomarkers of Barrett's Oesophagus

The use of metabolite profiles in patients with BO, a complication of GORD, has been studied. It was shown that creatinine and homocysteine were shown to be differentially expressed in patients with BO relative to those who had GORD; however, the multivariate model was associated with a lower receiver operator characteristic area under the curve.[68] Urinary metabolomics also revealed differences between healthy patients and those with BO. Eight metabolites were shown to have significantly different urinary concentrations between the BO and healthy patients, with sucrose and cis-aconitate showing the most significant differences among the two groups in regard to fold changes.[69] In WTC-PM-exposed firefighters, TNF-α, IFN-γ, induced protein-10, IL-6, and insulin, when elevated, were strongly associated with BO.[64] Further research is needed to continue to characterise the biomarker profile of GORD.

FURTHER NEED FOR RESEARCH

Although there are studies that demonstrate work-related risk factors of GORD,[70,71] the environment's role in GORD pathogenesis has been a neglected topic and PM-induced GORD is poorly understood. Conducting further studies on the prevalence of GORD in subjects who have been exposed to high PM concentrations or are in highly polluted areas can widen the evidence that environmental exposure is an independent risk factor for GORD.

The authors' lab is currently studying the effect of dietary intervention on WTC-PM-exposed

FDNY firefighters to determine its potential therapeutic effect on parameters such as FEV_1, fractional exhaled nitric oxide, and the metabolomic profile of those affected with WTC-associated lung disease, and whether these interventions can reduce the incidence of these conditions.

CONCLUSION

NCCP remains a highly prevalent complaint. With its financial cost, NCCP is an individual and societal burden. Despite the commonality and multifactorial nature of NCCP, the underlying mechanism of NCCP in the setting of PM exposure remains unexplained. The environment's role in the development of GORD and OAD is a dynamic topic that requires further research. Establishing a pathophysiologic basis of environmental exposure-associated NCCP may facilitate treatment and prevention.

References

1. Niska R et al. National hospital ambulatory medical care survey: 2007 emergency department summary. Natl Health Stat Report. 2010;(26):1-31.
2. Dumville JC et al. Non-cardiac chest pain: A retrospective cohort study of patients who attended a rapid access chest pain clinic. Fam Pract. 2007;24(2):152-7.
3. Eslick GD et al. Non-cardiac chest pain: Prevalence, risk factors, impact and consulting—A population-based study. Aliment Pharmacol Ther. 2003;17(9):1115-24.
4. Chambers JB et al. The head says yes but the heart says no: What is non-cardiac chest pain and how is it managed? Heart. 2015;101(15):1240-9.
5. Ford AC et al. Meta-analysis: The epidemiology of noncardiac chest pain in the community. Aliment Pharmacol Ther. 2011;34(2):172-80.
6. Maradey-Romero C, Fass R. New therapies for non-cardiac chest pain. Curr Gastroenterol Rep. 2014;16(6):390.
7. Safdar B et al. Chest pain syndromes are associated with high rates of recidivism and costs in young United States veterans. BMC Fam Pract. 2015;16:88.
8. Mourad G et al. Societal costs of non-cardiac chest pain compared with ischemic heart disease--A longitudinal study. BMC Health Serv Res. 2013;13:403.
9. Frieling T. Non-cardiac chest pain. Visc Med. 2018;34(2):92-6.
10. Esler JL, Bock BC. Psychological treatments for noncardiac chest pain: Recommendations for a new approach. J Psychosom Res. 2004;56(3):263-9.
11. Fass R, Achem SR. Noncardiac chest pain: Epidemiology, natural course and pathogenesis. J Neurogastroenterol Motil. 2011;17(2):110-23.
12. Kumar A, Cannon CP. Acute coronary syndromes: Diagnosis and management, part I. Mayo Clin Proc. 2009;84(10):917-38.
13. Mousavi S et al. Role of clinical presentation in diagnosing reflux-related non-cardiac chest pain. J Gastroenterol Hepatol. 2007;22(2):218-21.
14. Lee AL et al. Chronic pain in people with chronic obstructive pulmonary disease: prevalence, clinical and psychological implications. Chronic Obstr Pulm Dis. 2017;4(3):194-203.
15. Smeijers L et al. The independent association of anxiety with non-cardiac chest pain. Psychol Health. 2014;29(3):253-63.
16. Liu X et al. The effect of World Trade Center exposure on the timing of diagnoses of obstructive airway disease, chronic rhinosinusitis, and gastroesophageal reflux disease. Front Public Health. 2017;5:2.
17. Li J et al. Gastroesophageal reflux symptoms and comorbid asthma and posttraumatic stress disorder following the 9/11 terrorist attacks on World Trade Center in New York City. Am J Gastroenterol. 2011;106(11): 1933-41.
18. Karbasi A et al. Frequency distribution of gastro esophageal reflux disease in inhalation injury: A historical cohort study. J Res Med Sci. 2015;20(7):636-9.
19. Liu S et al. Association between exposure to ambient particulate matter and chronic obstructive pulmonary disease: Results from a cross-sectional study in China. Thorax. 2017;72(9):788-95.
20. Lytras T et al. Occupational exposures and 20-year incidence of COPD: The European Community Respiratory Health Survey. Thorax. 2018;73(11):1008-15.
21. Webber MP et al. Trends in respiratory symptoms of firefighters exposed to the World Trade Center disaster: 2001-2005. Environ Health Perspect. 2009;117(6):975-80.
22. Caraher EJ et al. Receptor for advanced glycation end-products and World Trade Center particulate induced lung function loss: A case-cohort study and murine model of acute particulate exposure. PloS One. 2017;12(9):e0184331.
23. Nolan A et al. Inflammatory biomarkers predict airflow obstruction after exposure to World Trade Center dust. Chest. 2012;142(2):412-8.
24. Hoffmann B et al. Chronic residential exposure to particulate matter air pollution and systemic inflammatory markers. Environ Health Perspect. 2009;117(8):1302-8.
25. Nazariah SS et al. Interleukin-6 via sputum induction as biomarker of inflammation for indoor particulate matter among primary school children in Klang Valley, Malaysia. Glob J Health Sci. 2013;5(4):93-105.
26. Dadvand P et al. Air pollution and biomarkers of systemic inflammation and tissue repair in COPD patients. Eur Respir J. 2014;44(3):603-13.
27. Canova C et al. PM10-induced hospital admissions for asthma and chronic obstructive pulmonary disease: The modifying effect of individual characteristics. Epidemiology. 2012;23(4):607-15.
28. Weiden MD et al. Biomarkers of World Trade Center particulate matter exposure: Physiology of distal airway and blood biomarkers that predict FEV1 decline. Semin Respir Crit Care Med. 2015;36(3):323-33.
29. Lee KY et al. Inter-alpha-trypsin inhibitor heavy chain 4: A novel biomarker for environmental exposure to particulate air pollution in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2015;10:831-41.

30. Nolan A et al. MMP-2 and TIMP-1 predict healing of WTC-lung injury in New York City firefighters. Respir Res. 2014;15:5.
31. Montano M et al. FEV1 inversely correlates with metalloproteinases 1, 7, 9 and CRP in COPD by biomass smoke exposure. Respiratory research. 2014;15:74.
32. Schenck EJ et al. Enlarged pulmonary artery is predicted by vascular injury biomarkers and is associated with WTC-Lung Injury in exposed fire fighters: A case-control study. BMJ Open. 2014;4(9):e005575.
33. Singh A et al. Predictors of asthma/COPD overlap in FDNY firefighters with World Trade Center dust exposure: A longitudinal study. Chest. 2018. [Epub ahead of print].
34. Cho SJ et al. YKL-40 is a protective biomarker for fatty liver in World Trade Center particulate matter-exposed firefighters. J Mol Biomark Diagn. 2014;5.
35. Tsukiji J et al. Lysophosphatidic acid and apolipoprotein A1 predict increased risk of developing World Trade Center-lung injury: A nested case-control study. Biomarkers. 2014;19(2):159-65.
36. Kwon S et al. Early elevation of serum MMP-3 and MMP-12 predicts protection from World Trade Center-lung injury in New York City firefighters: A nested case-control study. PLoS One. 2013;8(10):e76099.
37. Cho SJ et al. Chitotriosidase is a biomarker for the resistance to World Trade Center lung injury in New York City firefighters. J Clin Immunol. 2013;33(6):1134-42.
38. Weiden MD et al. Cardiovascular biomarkers predict susceptibility to lung injury in World Trade Center dust-exposed firefighters. Eur Respir J. 2013;41(5):1023-30.
39. Naveed B et al. Metabolic syndrome biomarkers predict lung function impairment: A nested case-control study. Am J Respir Crit Care Med. 2012;185(4):392-9.
40. Weiden MD et al. Obstructive airways disease with air trapping among firefighters exposed to World Trade Center dust. Chest. 2010;137(3):566-74.
41. Malik MA et al. Chest pain as a presenting complaint in patients with acute myocardial infarction (AMI). Pak J Med Sci. 2013;29(2):565-8.
42. Jerlock M et al. Pain characteristics in patients with unexplained chest pain and patients with ischemic heart disease. Eur J Cardiovasc Nurs. 2007;6(2):130-6.
43. Brady W, de Souza K. The HEART score: A guide to its application in the emergency department. Turk J Emerg Med. 2018;18(2):47-51.
44. Yau AA et al. The HEART pathway and hospital cost savings. Crit Pathw Cardiol. 2017;16(4):126-8.
45. Valadkhani S et al. Validation of the North American chest pain rule in prediction of very low-risk chest pain; a diagnostic accuracy study. Emerg (Tehran). 2017;5(1):e11.
46. Mathewkutty S et al. Biomarkers after risk stratification in acute chest pain (from the BRIC Study). Am J Cardiol. 2013;111(4):493-8.
47. Vaezi MF. Review article: The role of pH monitoring in extraoesophageal gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2006;23 Suppl 1:40-9.
48. Liuzzo JP, Ambrose JA. Chest pain from gastroesophageal reflux disease in patients with coronary artery disease. Cardiol Rev. 2005;13(4):167-73.
49. Park SH et al. Prevalence of gastrointestinal diseases and treatment status in noncardiac chest pain patients. Korean Circ J. 2015;45(6):469-72.
50. Dickman R et al. Prevalence of upper gastrointestinal tract findings in patients with noncardiac chest pain versus those with gastroesophageal reflux disease (GERD)-related symptoms: Results from a national endoscopic database. Am J Gastroenterol. 2007;102(6):1173-9.
51. Gomez Cifuentes J et al. Factors predictive of gastroesophageal reflux disease and esophageal motility disorders in patients with non-cardiac chest pain. Scand J Gastroenterol. 2018:53(6):643-9.
52. Lee AL, Goldstein RS. Gastroesophageal reflux disease in COPD: Links and risks. Int J Chron Obstruct Pulmon Dis. 2015;10:1935-49.
53. Tipnis NA et al. Distension during gastroesophageal reflux: Effects of acid inhibition and correlation with symptoms. Am J Physiol Gastrointest Liver Physiol. 2007;293(2):G469-74.
54. Min YW, Rhee PL. Esophageal hypersensitivity in noncardiac chest pain. Ann N Y Acad Sci. 2016;1380(1):27-32.
55. Herregods TVK et al. Determinants of the association between non-cardiac chest pain and reflux. Am J Gastroenterol. 2017;112(11):1671-7.
56. Wang HY et al. Prevalence of gastro-esophageal reflux disease and its risk factors in a community-based population in southern India. BMC Gastroenterol. 2016;16:36.
57. Eslick GD, Talley NJ. Gastroesophageal reflux disease (GERD): Risk factors, and impact on quality of life-a population-based study. J Clin Gastroenterol. 2009;43(2):111-7.
58. Qureshi Z et al. Occupational exposure and the risk of Barrett's esophagus: A case-control study. Dig Dis Sci. 2013;58(7):1967-75.
59. Bordoni B et al. Chest pain in patients with COPD: The fascia's subtle silence. Int J Chron Obstruct Pulmon Dis. 2018;13:1157-65.
60. Janssen DJ et al. Prevalence of thoracic pain in patients with chronic obstructive pulmonary disease and relationship with patient characteristics: A cross-sectional observational study. BMC Pulm Med. 2016;16:47.
61. Aldrich TK et al. Lung function in rescue workers at the World Trade Center after 7 years. N Engl J Med. 2010;362(14):1263-72.
62. Kim HJ et al. Predictive and prognostic biomarkers of respiratory diseases due to particulate matter exposure. J Cancer Prev. 2017;22(1):6-15.
63. Ling SH, van Eeden SF. Particulate matter air pollution exposure: Role in the development and exacerbation of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2009;4:233-43.
64. Haider SH et al. Predictive biomarkers of gastroesophageal reflux disease and Barrett's esophagus in World Trade Center exposed firefighters: A 15 year longitudinal study. Sci Rep. 2018;8(1):3106.
65. Zeig-Owens R et al. Blood leukocyte concentrations, FEV1 decline, and airflow limitation. A 15-year longitudinal study of World Trade Center-exposed firefighters. Ann Am Thorac Soc. 2018;15(2):173-83.
66. Kia L et al. Biomarkers of reflux disease. Clin Gastroenterol Hepatol. 2016;14(6):790-7.
67. Kandulski A et al. Proteinase-activated receptor-2 in the pathogenesis of gastroesophageal reflux disease. Am J Gastroenterol. 2010;105(9):1934-43.
68. Buas MF et al. Candidate serum metabolite biomarkers for differentiating gastroesophageal reflux disease, Barrett's esophagus, and high-grade dysplasia/esophageal adenocarcinoma. Metabolomics. 2017;13(3):pii:23.
69. Davis VW et al. Urinary metabolomic signature of esophageal cancer and Barrett's esophagus. World J Surg Oncol. 2012;10:271.
70. Pregun I et al. Gastroesophageal reflux disease: Work-related disease? Dig Dis. 2009;27(1):38-44.
71. Jang SH et al. Psychological factors influence the gastroesophageal reflux disease (GERD) and their effect on quality of life among firefighters in South Korea. Int J Occup Environ Health. 2016;22(4):315-20.

Pathology and Pathogenesis of Radiation Bowel Disease: Histopathological Appraisal in the Clinical Setting

Authors: *Najib Haboubi

Professor of Health Sciences and Liver and Gastrointestinal Pathology, Spire Healthcare Trust, Manchester, UK
*Correspondence to najibhaboubi@hotmail.com

Disclosure: The author has declared no conflicts of interest.

Received: 23.08.18

Accepted: 06.11.18

Keywords: Disease, intestine, radiation, radiation bowel disease (RBD).

Citation: EMJ Gastroenterol. 2018;7[1]:113-119.

Abstract

Over the last half century, radiotherapy has been established as a very effective treatment modality for solid tumours. Large numbers of patients owe their lives to this treatment; however, radiotherapy is not without a price. When applied to the pelvic organs, radiotherapy carries potential serious complications, including in the small and large bowels. This article describes the magnitude of the clinical and social problems of radiation bowel disease, presents the histopathological features, and puts these features in the clinical context of the condition. The article will not address prevention and management for radiation bowel disease nor complications outside the gastrointestinal tract.

INTRODUCTION

A crucial step in the proper management of a patient with any disease is the consideration of therapy risks against its benefits. In cancer patients, clinicians are faced with the task of weighing up the benefit of prolonged, and hopefully complication-free, survival following surgery and/or chemotherapy and/or radiotherapy versus the risks of treatment-related complications. Ionising radiation is the mainstay therapy for a host of solid malignancies of the rectum, prostate, and lower urological and female reproductive systems.

As the number of cancer survivors continues to increase, the long-term outcomes related to health and wellbeing, exemplified by those patients who develop radiation bowel disease (RBD), become a focal point in health issues; therefore, there is an urgent need for a serious evaluation of prevention and management of RBD. More people with pelvic tumours are treated with radiotherapy than those with tumours at any other anatomical site and as more people live longer with cancer, the burden of RBD increases.[1] It is estimated that today >3-times as many people survive cancer than 40 years ago, largely as a result of more successful multimodality therapy.[1] However, up to 25% of cancer survivors report a decline in quality of life secondary to radiotherapy,[2] notwithstanding the large cohort of patients who do not report the complications as they accept the condition(s) as part of cancer treatment success.

RBD results from therapy-induced damage to surrounding non-cancerous tissues, which leads to changes in the normal physiological functions of the various organs, including the small and large bowel. Treating the pelvis with radiotherapy renders the bowel at risk of radiation-induced injury, which is a condition known by the recently coined term pelvic radiation disease.[1,3,4] The term denotes conditions such as radiation enteritis, radiation proctitis, and radiation cystitis.[5] This article will be confined to RBD.

The initial stages of RBD involve damage to the epithelial tissue, a process that triggers an inflammatory response. For those patients who go on to develop RBD, this process will be followed by progressive ischaemia and fibrosis. The radiation damage to healthy tissue around the tumour can be responsible for treatment interruption.

A questionnaire investigating the opinion of clinical oncologists in the UK showed that most believe that RBD is an under-recognised and inadequately managed serious problem.[6] Indeed, one study estimated that the annual incidence of patients adversely affected by RBD is greater than the number of patients diagnosed with Crohn's disease.[7] Several studies have shown significant complications in patients with pelvic tumours treated with surgery alone or surgery combined with either preoperative short or long-course, or postoperative, radiotherapy.[8-10]

As for the frequency of RBD, one study showed that 9 out of 10 patients who received pelvic radiotherapy experienced a chronic change to their bowel habits, with 5 out of 10 reporting a significant change to their quality of life.[11]

Not all patients who receive radiotherapy directed at tumours within the pelvis develop RBD. The reason for this is unclear; however, evidence suggests it may be a multifactorial process involving patient-related and treatment-related factors.

THE CLINICAL PRESENTATION

There is a huge range of clinical presentations of RBD owing to numerous influential variables, such as timing of radiotherapy, site of tissue damage, severity of tissue damage, side effects of medications, coexisting medical conditions, and psychological issues. The clinical presentations can be crudely classified into three phases: acute, chronic, and delayed (latent).[12]

Within these groups, the symptoms of RBD may manifest as a result of direct damage to pelvic structures or as secondary phenomena triggered by the radiotherapy. These phenomena include small bowel bacterial overgrowth, bile salt malabsorption, malabsorption of lactose, and similar fermentable sugars.[13]

The Acute Phase

Acute RBD is defined as an acute inflammatory reaction to radiation treatment that can occur during, immediately after, or within the first 3 months of radiotherapy. RBD occurs in 60–80% of patients treated with abdominal or pelvic radiotherapy and is a major risk factor for modification of the planned treatment regimen; such changes can have ramifications on local tumour control.[14] Common symptoms of RBD include nausea, bloating, diarrhoea, tenesmus, abdominal cramps, urinary urgency, mucus discharge, faecal urgency, loss of appetite, and bleeding. Such non-specific symptoms are usually self-limited within 3 months but can overlap with other conditions, such as infection, which need to be excluded. Bleeding occurs in ≤50% of patients.[4]

Symptoms of acute RBD most commonly manifest in the second week post-radiotherapy and peak in Week 4 or 5 and resolve within 2–6 months.[13] Importantly, the occurrence of acute RBD does not necessarily increase the risk of developing chronic RBD later on and patients can be reassured that resolution of symptoms generally occurs with cessation of radiotherapy.[15]

The Chronic Phase

Chronic RBD is a progressive condition and major cause of morbidity for cancer survivors. Symptoms of chronic RBD begin to develop after a period of 6 months to 3 years post treatment, but can occur up to three decades following treatment. Clinically, the signs of chronic RBD are symptoms of bowel dysmotility, such as urgency incontinence, change in bowel habits, and malabsorption.[14] In fact, when treating rectal cancer with radiation, it has been

estimated that the majority of patients will present with faecal incontinence.[16]

Vascular telangiectasia often leads to bleeding in the chronic phase. The timing of radiotherapy in relation to symptom manifestation is key to raising clinical suspicion and providing tailored support for RBD. Patients who experience long-standing chronic RBD can also experience sudden complications, such as bowel obstruction due to stricture formation, adhesions, fissures, severe bleeding, and perforation. Surgeons should be alert to the fact that RBD may be the cause of acute or subacute small bowel obstruction.

The Latent Phase

The third stage of the clinical pathological presentation of RBD is rare but well recognised. Latent-phase symptoms are in fact those of secondary malignancies, which can arise within or outside of the irradiation field years or decades after the initial radiotherapy treatment. Radiotherapy used to treat the first malignancy can induce minor alterations to the nuclear DNA that predispose the cell to novel DNA mutations, carcinogenesis, and teratogenesis.[12] One study aimed to explain the association between radiotherapy and secondary malignancies by looking at the genetic profile of the non-cancerous mucosa. The researchers found aneuploidy in some cases that showed subtle epithelial nuclear changes in the irradiated field.[17]

Clinicians should be suspicious of a new tumour in any patient who has received pelvic radiotherapy and has new onset symptoms of cancer, such as rectal bleeding. Furthermore, although the risk of secondary malignancies after pelvic radiotherapy is modestly increased compared to the overall population, patients should be informed about the risk. However, some experts regard the latent phase as a complication and not necessarily a phase.

PREDISPOSING FACTORS

Predisposing factors can be broadly divided into host factors and therapy factors.[12] Host factors include diabetes, atherosclerosis, hypertension, and smoking, which are all factors that accelerate the process, particularly late-phase disease, which starts as a progressive vascular phase and ends with the fibrotic phase.

The therapeutic factors that are associated with a high risk of developing RBD include high-dose radiation; a large irradiation field; timing, as postoperative radiation is more toxic than preoperative radiation; concomitant chemotherapy; and prior abdominal surgery, which leads to entrapment of the small intestine in the pelvis with similar effect of adhesion and prolapse of abdominal organs into the pelvis.[1,12]

THE PATHOPHYSIOLOGY OF RADIATION BOWEL DISEASE

Cells exposed to ionising radiation experience oxidative stress injuries. The damage is widespread; however, the principal subcellular target is the nuclear DNA.[1]

Both direct and indirect mechanisms inhibit DNA from fulfilling its function as a template for DNA transcription. The nuclear chromatin is directly targeted, causing DNA damage through the generation of inter and intra-strand cross-linkages, breaks, and mutations. The plasma membrane is directly affected, as radiotherapy disrupts the rigidity of the phospholipid bilayer and electric gradient. These types of injuries challenge the integrity of the cell. Indirect damage develops secondary to the formation of free radicals from the ionisation of water molecules.[12] While the radiation damage is in progress, at the same time, intricate and co-ordinated DNA repair mechanisms have evolved to fix damage induced by ionising radiation, which includes strand breaks and replication errors.[18] At low levels of radiation, repair mechanisms in the cell can resolve injuries, such as double-strand breaks. With increasing amounts of radiation, the damage inflicted overwhelms these systems and either the cell enters programmed cell death (apoptosis) or mitosis is inhibited. The amount of ionising radiation required to inflict cell inactivation and cell death varies between each tumour and its surrounding tissues.[1,18]

A further variable that influences a cell's response to radiotherapy is whether adjuvant chemotherapy is included in therapy. Concomitant chemotherapy often leads to delay or prevention of the reparative process,

thus aggravating the disease. The timing of radiotherapy in relation to chemotherapy is an essential consideration.[19]

The damaging effect of radiotherapy is most potent against tissues with high cellular turnover,[3] making it ideal for treating rapidly proliferating tumour cells. This is because the potential cell injury is dependent not only on the cellular repair processes but also the stage of the cell cycle that the cell is in.

The following simplified schedule shows the relation between primary tissue type damage, phase of RBD, and the timescale of RBD symptoms:

- Acute proctitis: epithelial phase: 0–4 weeks.
- Acute enteritis: epithelial phase: 0–4 weeks.
- Rectal bleeding: vascular phase: 4–12 months.
- Anal or perianal pain: stromal phase: 6–9 months.
- Chronic abscess: stromal phase: 9–15 months.
- Fistula: stromal phase: 18–24 months.
- Stricture or malabsorption: stromal phase: 2–20 years.
- Rectal malignancy: latent epithelial phase: 5–30 years.

Certain stages within the cell cycle optimise the opportunity to repair damage. For example, ionising radiation damage results in cell cycle arrest and initiation of a temporary cell cycle checkpoint. This aims to provide time to conduct repairs. A crucial protein in the checkpoint machinery is the tumour suppressor p53. Highly proliferative cells, such as those residing in the crypt epithelium of the bowel, are frequently in the more radiosensitive G2–M phases of the cell cycle.[19] Crypt cell death results in insufficient renewal of the villous epithelium. The mucosa and lamina propria become inflamed and the mucosal barrier breaks down. In comparison, slowly dividing tissues, such as those in vascular or fibrous tissue, spend more time in the less radiosensitive G1 and S phases and damage to these tissues is usually not responsible for acute clinical presentations.[20]

Impaired ano-rectal functionality is an important problem in RBD. Maintenance of faecal continence is regulated by the tonic contractions of the internal and external anal sphincters. The former is a smooth muscle supplied by intrinsic myenteric innervation and has the primary role of maintaining a tonic contraction and, thus, continence while at rest. By contrast, the external sphincter is composed of striated muscle and is innervated by an extrinsic supply. The internal and external sphincters work together to provide an effective seal to solids, liquids, and flatus. The ano-rectum has a rich nervous supply, which includes pain, temperature, and touch sensory components, each of which aid the maintenance of continence through the ability to differentiate between solids and flatus. Impaired anal functioning can result from damage to the nerves of the pelvis, including the pudendal nerve, the lumbo-sacral plexus, and the myenteric plexus. The external anal sphincter is relatively radio-resistant and it is postulated that faecal incontinence is strongly influenced by nerve damage. Case reports have demonstrated that damage to the pudendal nerve may lead to morphological changes in the muscle. Some case reports have proposed that injury to the lumbo-sacral plexus can indirectly affect the external anal sphincter by causing perianal anaesthesia.[20]

As chemoradiotherapy or radiotherapy alone often accompanies surgery in the treatment of rectal cancer, such a combination adds to the physiological disruption of normal ano-rectal function, and this needs to be factored in and communicated to the patient when such a therapy is indicated.[21,22]

MICROSCOPIC CHANGES TO THE BOWEL MUCOSA

An appreciation of the radiation-induced microscopic changes observed in patients with RBD provides insights into understanding the clinical symptoms, stages of the disease, and how best to manage the condition. The epithelial cells within the bowel wall, particularly those in the small bowel, have a high turnover rate, which renders them vulnerable to ionising radiation. There is a fine balance between the dose tolerated by the epithelium and the dose that destroys the neoplasm.

Histologically, the damage inflicted on surrounding healthy tissues has characteristic appearances. There are three main histological

phases depending on the tissue type that is predominantly affected. The epithelial phase generally correlates with acute-phase clinical symptoms, with vascular and then stromal changes commencing several weeks later.[22] Later on, the fibrotic phase complicates the picture.

In the epithelial phase, damage to the epithelium, seen as sloughing of epithelial cells into the crypt lumina, can be observed within 8 hours of exposure to ionising radiation.[1] The characteristic acute-phase histological changes are epithelial meganucleosis and significant eosinophilic infiltrate with formation of eosinophilic microabscesses (Figure 1). Caution and experience are required to interpret these morphological changes because they can resemble dysplasia. Nuclear and cytoplasmic early-phase changes are usually reversible.[23] Mitosis is inhibited, which prevents epithelial regrowth and causes epithelial denudation. Importantly, during the acute phase, the vasculature appears normal.[23] The vascular phase follows the epithelial phase, which is characterised by telangiectasia of capillaries and post-capillary venules, fibrin deposition, subendothelial oedema, and platelet thrombi formation that can cause rectal bleeding.[12] Ultimately, there is significant narrowing of the vascular lumina, which leads to ischaemia and fibrosis (Figure 2). Macroscopically, these microscopic changes correlate with a pale, non-compliant bowel wall with telangiectasia.[15]

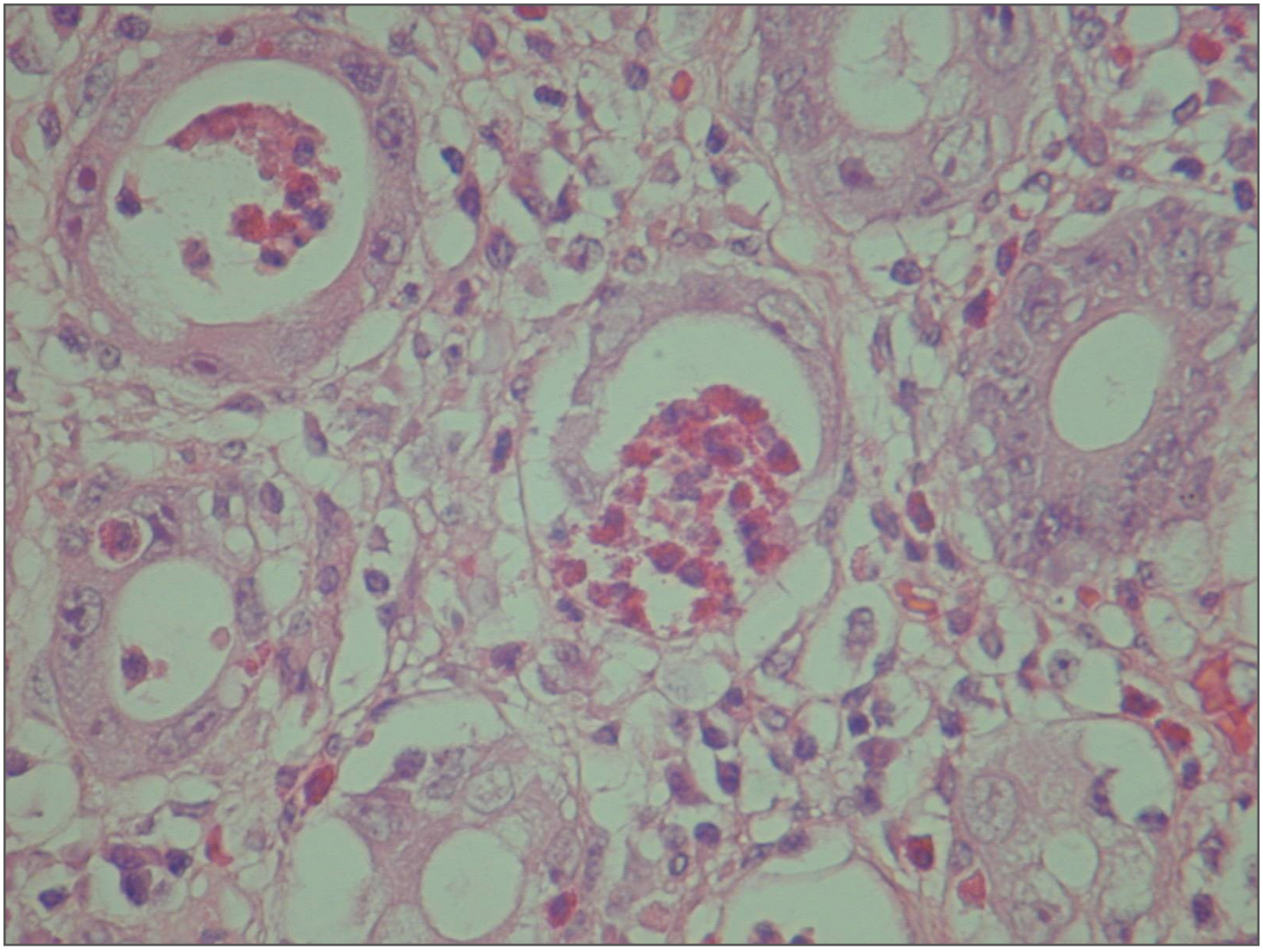


Figure 1: Eosinophilic crypt abscess with meganucleosis characteristics of an acute-phase reaction.

The nuclear abnormality should not be confused with dysplasia.

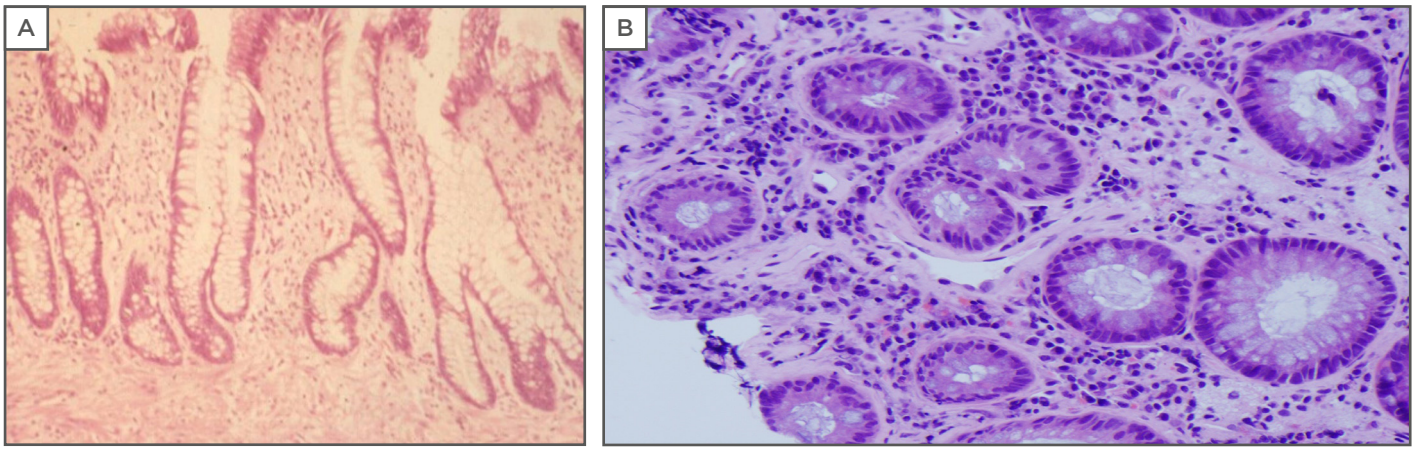


Figure 2: A) Crypt distortion and fibrosis of the lamina propria in a chronic-phase reaction mimicking chronic inflammatory bowel disease. B) Vascular telangiectasia in a chronic-phase reaction, a cause of frequent rectal bleeding.

The reversibility of the vascular phase morphological changes is unclear; however, the stromal phase, which includes mesenchymal and stromal fibrosis, is irreversible.[23,24] The third phase is the fibrotic mesenchymal phase, which is a progressive phenomenon that follows and is caused by vascular damage. Fibrosis of the lamina propria leads to crypt distortion.

Despite these distinctions, the bowel has a limited array of modifications in response to damage. In fact, under a microscope the quiescent phase of inflammatory bowel disease looks the same as chronic RBD. Since chronic RBD can take months if not years to develop, it is quite possible that RBD is overlooked as a differential diagnosis and the histopathologist could remain oblivious to the patient's history of irradiation. Relevant clinical information is therefore essential for the histopathologist; as they work through numerous rectal biopsies labelled with minimal clinical information, the biopsy from the patient with chronic RBD could be mistaken for chronic inflammatory bowel disease.[25]

Importantly, a study profiling the time patterns of histological mucosal changes in relation to the clinical manifestation of RBD indicated that they do not always coincide.[26] Microscopic evidence of inflammation in rectal biopsies precedes the onset of symptoms. Thus, pathological changes do not always cause the symptoms, but it is the disruption to normal physiological processes that results in the symptoms such as diarrhoea and incontinence. These findings suggest that pre-emptive, prophylactic treatment to prevent RBD may be a prudent way to tackle the condition.[26]

References

1. Morris K, Haboubi NY. Pelvic radiation therapy: Between delight and disaster. World J Gastrointest Surg. 2015;7(11):279-88.
2. Armes J et al. Patients' supportive care needs beyond the end of cancer treatment: A prospective, longitudinal survey. J Clin Oncol. 2009;27(36):6172-9.
3. Andreyev HJ et al.; British Society of Gastroenterology; Association of Colo-Proctology of Great Britain and Ireland; Association of Upper Gastrointestinal Surgeons; Faculty of Clinical Oncology Section of the Royal College of Radiologists. Practice guidance on the management of acute and chronic gastrointestinal problems arising as a result of treatment for cancer. Gut. 2012;61(2):179-92.
4. Andreyev HJ et al. "Pelvic radiation disease": New understanding and new solutions for a new disease in the era of cancer survivorship. Scand J Gastroenterol. 2011;46(4):389-97.
5. Suresh UR et al. Radiation disease of the urinary tract: Histological features of 18 cases. J Clin Pathol. 1993;46(3):228-31.
6. Henson CC et al. Late-onset bowel dysfunction after pelvic radiotherapy: A national survey of current practice and opinions of clinical oncologists.

Clin Oncol (R Coll Radiol). 2011;23(8):552-7.

7. Denham JW, Hauer-Jensen M. Radiation induced bowel injury: A neglected problem. Lancet. 2013;382(9910):2046-7.
8. Sauer R et al.; German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;35(17)1:1731-40.
9. Birgisson H et al. Late gastrointestinal disorders after rectal cancer surgery with and without preoperative radiation therapy. Br J Surg. 2008;95(2):206-13.
10. Peeters KC et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: Increased bowel dysfunction in irradiated patients—A Dutch colorectal cancer group study. J Clin Oncol. 2005;23(25):6199-206.
11. Olopade FA et al. A modified Inflammatory Bowel Disease questionnaire and the Vaizey Incontinence questionnaire are simple ways to identify patients with significant gastrointestinal symptoms after pelvic radiotherapy. Br J Cancer. 2005;92(9):1663-70.
12. Haboubi NY et al. Radiation bowel disease: Pathogenesis and management. Colorectal Dis. 2000;2(6):322-9.
13. Stacey R, Green JT. Radiation-induced small bowel disease: Latest developments and clinical guidance. Ther Adv Chronic Dis. 2014;5(1):15-29.
14. Hauer-Jensen M et al. Radiation enteropathy—Pathogenesis, treatment and prevention. Nat Rev Gastroenterol Hepatol. 2014;11(8):470-9.
15. Do NL et al. Radiation proctitis: Current strategies in management. Gastroenterol Res Pract. 2011;2011:917941.
16. Chen TYT et al. Bowel dysfunction after rectal cancer treatment: A study comparing the specialists versus patient's perspective. BMJ Open. 2013;4:e003374.
17. Pearson JM et al. Flow cytometric DNA characteristics of radiation colitis—A preliminary study. Anticancer Res. 1992;12(5):1647-9.
18. Metheetrairut C, Slack FJ. MicroRNAs in the ionizing radiation response and in radiotherapy. Curr Opin Genet Dev. 2013;23(1):12-9.
19. Pawlik TM, Keyomarsi K. Role of cell cycle in mediating sensitivity to radiotherapy. Int J Radiat Oncol Biol Phys. 2004;59(4):928-42.
20. Bondeven P et al. Neoadjuvant therapy abolishes the functional benefits of a larger rectal remnant, as measured by magnetic resonance imaging after restorative rectal cancer surgery. Eur J Surg Oncol. 2015;41(11):1493-9.
21. Bregendahl S et al. Bowel dysfunction after low anterior resection with and without neoadjuvant therapy for rectal cancer: A population-based cross-sectional study. Colorectal Dis. 2013;15(9):1130-9.
22. Putta S, Andreyev HJ. Faecal incontinence: A late side-effect of pelvic radiotherapy. Clin Oncol (R Coll Radiol). 2005;17(6):469-77.
23. Haboubi NY et al. The light and electron microscopic features of early and late phase radiation-induced proctitis. Am J Gastroenterol. 1988;83(10):1140-4.
24. Berthrong M, Fajardo LF. Radiation injury in surgical pathology. Part II. Alimentary tract. Am J Surg Pathol. 1981;5(2):153-78.
25. Haboubi NY et al. Radiation colitis is another mimic of chronic inflammatory bowel disease. J Clin Pathol. 1992;45(3):272.
26. Larsen A et al. Time patterns of changes in biomarkers, symptoms and histopathology during pelvic radiotherapy. Acta Oncol. 2007;46(5):639-50.

Prevention of Infantile Colic Using Probiotics

Authors: *Hamid Ahanchian,[1,2] Asma Javid[3]

1. Children's Health and Environment Program, Queensland Children's Medical Research Institute, University of Queensland, Brisbane, Australia
2. Department of Allergy and Immunology, Mashhad University of Medical Sciences, Mashhad, Iran
3. Department of Pediatrics, Mashhad University of Medical Science, Mashhad, Iran

*Correspondence to h.ahanchian@uq.edu.au

Disclosure: The authors have declared no conflicts of interest.

Received: 31.08.18

Accepted: 24.10.18

Keywords: Infantile colic (IC), prevention, probiotics, synbiotic.

Citation: EMJ Gastroenterol. 2018:7[1]:120-127.

Abstract

Objective: Infantile colic is a frustrating impasse that affects up to 20% of infants. Even though its pathogenesis is currently unknown, some hypotheses are food hypersensitivity or allergy, gut dysmotility, inflammation, and visceral pain. The use of probiotics in treatment and prevention of infantile colic is a relatively new topic.

Method: Literature searches were conducted using Ovid MEDLINE®, EMBASE®, and the Cochrane Central Register of Controlled Trials. Randomised controlled trials including the terms "neonate(s)", "infant(s)", "probiotics", "synbiotics", "*Lactobacillus*", "*Bifidobacterium*", "colic", and "prevention" were included.

Results: Three studies showed the different composition of intestinal microbiota between colicky infants and control groups. In six of the studies, probiotic and/or synbiotic supplementation significantly decreased the rate of crying and pain in colicky infants compared with placebo; however, in two studies, no effect on the incidence and frequency of colic-related restlessness was detected. In all, the reviewed studies demonstrated that probiotic and/or symbiotic treatment regimens were effective for infantile colic prevention.

Conclusions: There is much evidence suggestive of diversity in the intestinal microbiota among colicky and healthy infants. Based on recent research, using probiotics and synbiotics is a practical and favourable strategy for prevention and treatment of fussiness in colicky infants.

INTRODUCTION

Infantile colic (IC) is defined as paroxysms of crying or fussing due to abdominal pain for ≥3 hours a day, occurring 3 days or more per week for 3 weeks, in a healthy infant aged from 2 weeks to 3 months.[1,2] IC's prevalence is estimated to be up to 20% in the general population and is well-known as a frustrating problem among parents and healthcare professionals.[3] The condition usually manifests at about 2 weeks of age and no longer exists by 4 months of age.

Although the pathogenesis of IC is presently unknown, it is likely due to a multitude of factors, with many theories proposed. Psychosocial

theories, such as inadequate maternal–infant interactions, family tension, maternal anxiety, depression, and smoking, are potentially risk factors.[4,5] Gastrointestinal hypotheses mention increased intra-abdominal gas, visceral pain, and immaturity of the nervous or digestive system.[4,6]

Despite there being several benign treatment modalities available, there is no gold standard treatment option for colicky infants. The current management technique recommended is the provision of support and reassurance to the parents,[7-10] although, in breast-fed infants, the use of hypoallergic foods and the exclusion of cow's milk protein from the mother's diet has been suggested.[7-9,11] In bottle-fed infants, using hypoallergenic formulas was shown to be effective in a few studies.[7,8,12]

Pharmaceutical treatment has limited benefit in the management of colicky pain. While agents such as dicyclomine, simethicone, and nutritional supplements can be useful in some infants, few randomised controlled trials (RCT) support their efficacy.[13-15] Currently, recent evidence has suggested probiotic and synbiotic usage for the improvement of colicky pain.[16,17]

While the need to find a treatment for infantile colic may not appear immediately obvious because of the condition's benign and ultimately self-resolving nature, infantile colic can increase the risk of maternal depression,[18] early breastfeeding discontinuance,[19] and shaken baby syndrome.[20] In this context, the imperative to develop a viable therapeutic option becomes more pressing.

Ancient physicians in the Middle East used yogurt for curing disorders of the stomach and intestines.[21] In the Persian variant of the Old Testament, it is stated that "Abraham owed his longevity to the consumption of sour milk" (Genesis 8:18).[22]

In 1908, the Russian scientist Elie Metchnikoff proposed that the long life of Bulgarian peasants came from their consumption of fermented milk products, and this theory has led to the increasing popularity of probiotics and intestinal microbiota research.[21]

In 2001, a joint Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) expert consultation defined probiotics as 'live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host.'[23] Prebiotics are defined as 'non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, thus improving host health.'[24] Synbiotics are products that contain both probiotic and prebiotic components.

Previous studies have shown the safety of probiotic and synbiotic medications in healthy children.[25] In 2014, a study analysing 57 clinical trials that administered probiotics and synbiotics to infants between 0 and 24 months old found there were no major adverse effects.[26] Diarrhoea, vomiting, and bloating are the most common adverse effects.[27,28] Because of limited evidence, probiotic administration in high-risk groups (such as preterm infants and immune deficient children) may be contraindicated.[29,30]

Gut–Brain Axis and Microbiota

The intestine of a newborn infant is essentially sterile, and early postnatal life is known as the bacterial colonisation phase. The main sources of the colonising bacteria are the mother and the environment.[31,32] The collection of genomes of these microbes is recognised as the human microbiome.[33]

The presence of these microbiota is crucial for the infant's physiology, including the evolution of the gastrointestinal (GI) tract and health of the immune system. Recent studies have also revealed the requirement of gut microbiota for the normal functioning of the central nervous system (CNS).[34,35]

As mentioned, gut microbiota consist of various communities of bacteria and their structure and activity have recently been better identified through the use of molecular and metagenomics tools. Lots of bacterial phyla are present in the GI tract, such as Actinobacteria, Bacteroidetes, Firmicutes, Fusobacteria, Proteobacteria, and Verrucomicrobia,[36] with Bacteroidetes and Firmicutes accounting for 70–75% of microbiomes.[36,37]

Genetics, prematurity, mode of delivery,[10] age, diet, metabolism, geographic region, stress, and probiotic or antibiotic consumption are factors that can impact the infant microbiome.[38-40]

An adult human intestine contains about 100 trillion necessary bacteria,[32] and by 2 years of age the child's gut microbial profile begins to look more like that of an adult.[25]

Currently, many studies support the functional link between the GI tract and the CNS[41]; this is referred to as the gut–brain axis (GBA). This complex consists of the hypothalamic pituitary adrenal axis, CNS, the autonomic nervous system, and the enteric nervous system.[42] The central nervous system and, in particular, the hypothalamic pituitary adrenal axis, can be activated in response to environmental factors, such as changes in emotion or stress. The hypothalamic pituitary adrenal axis stimulates cortisol release and is driven by a complex interaction between the amygdala, hippocampus, and hypothalamus, which constitute the limbic system. Hypothalamic secretion of the corticotropin-releasing factor stimulates adrenocorticotropic hormone secretion from the pituitary gland that, in turn, leads to cortisol release from the adrenal glands. In parallel, the central nervous system communicates along both afferent and efferent autonomic pathways, with different intestinal targets, such as the enteric nervous system, muscle layers, and gut mucosa, modulating motility, immunity, permeability, and secretion of mucus. The enteric microbiota has a bidirectional communication with these intestinal targets, modulating gastrointestinal functions and being itself modulated by brain–gut interactions.[42]

Thus, the gut–brain axis is associated with involvement in the pathogenesis of certain CNS disorders, such as autism spectrum disorders,[43] anxiety, depression,[44] and chronic pain.[31]

Information transport between the GI tract and the brain takes place via four major pathways:

- Vagal and spinal afferent neurons.
- Immune system signalling.
- Endocrine signalling.
- Microbial factors.[43,45,46]

These pathways are closely associated with each other.[47]

In many of these communication pathways, the important role of the biologically active gut peptides and neuropeptides are clear. Manipulation of the microbiota with antibiotics,[48] probiotics, synbiotics, functional foods,[49] and also faecal microbial transplantation[50] and germ-free animal models,[51] has shown the important role of gut microbiota–brain interactions.[42]

There is evidence suggestive of diversity in intestinal microbiota among colicky and healthy infants,[52] with lower biodiversity in the stool microbiota of colicky infants, including a diminished number of lactobacilli and greater counts of Gram-negative bacteria.[52]

In this review, the authors discuss the literature on using probiotics for the treatment of infant colic, and then shift their focus to recent trials focussing on prevention of infant colic via prebiotic, probiotic, and symbiotic interventions.

METHODS

Search Strategy

Eligible studies published between January 1966 and August 2018 were identified from within the National Library of Medicine. Many databases were searched, including Ovid MEDLINE®, EMBASE®, and the Cochrane Central Register of Controlled Trials. A number of search terms were used: "neonate(s)", "infant(s)", "probiotics", "synbiotics", "*lactobacillus*", "*Bifidobacterium*", "colic", and "prevention". There was no language restriction to the search.

Study Selection

All RCT that compared probiotics to placebo or other forms of treatment in healthy infants <4 months of age were included. All definitions of infantile colic were accepted. Articles in any language were considered as long as there was an abstract in English indicating content.

Data Extraction

Reviewers assessed eligibility of retrieved articles and abstracted descriptive data on the subjects, type of intervention, outcomes, and methodological quality. Miscalculations were resolved by consensus and discussion.

Methodological Quality of the Studies

To determine the methodological quality of selected trials, the standard methods of the Cochrane Collaboration were used.

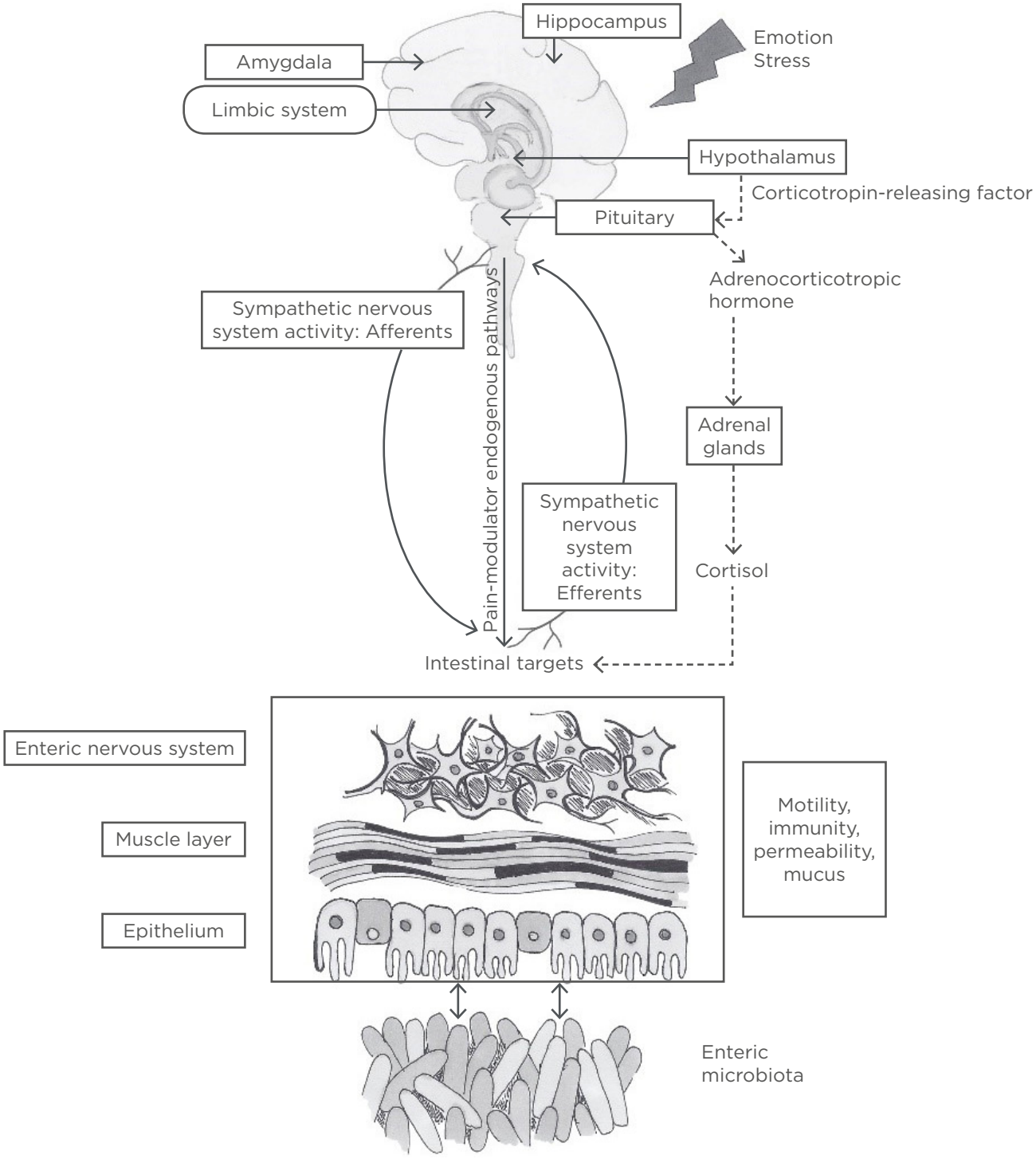


Figure 1: The role of the gut microbiome in the gut-brain axis.

The central nervous system and, in particular, the hypothalamic pituitary adrenal axis (represented by the dashed line), can be activated in response to environmental factors, such as changes in emotion or stress. The hypothalamic pituitary adrenal axis stimulates cortisol release and is driven by a complex interaction between amygdala, hippocampus, and hypothalamus, which constitute the limbic system. Hypothalamic secretion of the corticotropin-releasing factor stimulates adrenocorticotropic hormone secretion from the pituitary gland that, in turn, leads to cortisol release from the adrenal glands. In parallel, the central nervous system communicates along both afferent and efferent autonomic pathways, with different intestinal targets, such as the enteric nervous system, muscle layers, and gut mucosa, modulating motility, immunity, permeability, and secretion of mucus. The enteric microbiota has a bidirectional communication with these intestinal targets, modulating gastrointestinal functions and being itself modulated by brain–gut interactions.[42]

Table 1: Comparison of studies examining the use of probiotics and/or synbiotics for infantile colic.

Author	Study design	Main results
Lehtonen et al.,[53] 1994	Descriptive-analytical study	Disparity in the gut microbiota have been reported between colicky and non-colicky infants.
de Weerth et al.,[52] 2013	Descriptive-analytical study	A reduction in butyrate-producing bacteria promotes intestinal inflammation and pain.
Roos et al.,[58] 2013	Randomised, double blinded, placebo-controlled study	A decrease in colicky symptoms was related to the changes of the gut microbiota.
Kianifar et al.,[16] 2014	Randomised, double blinded, placebo-controlled study	Successful treatment (reduction in crying time) in the synbiotic group.
Savino,[61] 2010	Randomised, double blinded, placebo-controlled study	Significantly less crying in the treatment group.
Szajewska et al.,[62] 2013	Randomised, double blinded, placebo-controlled study	Exclusively or predominantly breastfed colicky infants benefit from *Lactobacillus reuteri* DSM 17938 administration.
Saavedra et al.,[17] 2004	Randomised, double-blind, placebo-controlled study. Prophylactic intervention.	Formula containing two strains of probiotic (*Bifidobacterium lactis* and *Streptococcus thermophiles*) reduced irritability of colicky infants.
Anabrees et al,[63] 2013	Review of three studies.	Probiotic supplementation notably decreased the rate (minutes per day) of crying and pain.
Ben et al.,[64] 2008	Descriptive-analytical study	Did not show benefits of probiotics in colicky infants.
Mugambi et al.,[65] 2012	Review of three studies using synbiotic formula in infancy.	Synbiotics had no effect on incidence and frequency of colic restlessness.

For each trial, information was pursued regarding the method of randomisation, allotment concealment, blinding, and complete follow-up, as well as noted outcomes of all studied infants. The methodological details of the studies were extracted from published data.

RESULTS

Probiotics for the Treatment of Infantile Colic

Lots of evidence shows the different composition of intestinal microbiota between colicky infants and control groups. In some studies, a difference in the gut microbiota has been reported.[53-56] Some studies have shown an increase in the number of pathogenic bacteria and a reduction in butyrate-producing bacteria, thus promoting intestinal inflammation and pain.[16,52,57]

One RCT compared the microbial composition in faecal samples of colicky infants receiving *L. reuteri* or placebo. Roos et al.[58] concluded that increasing Bacteroidetes levels in responder infants determined a decrease in colicky symptoms related to the changes of the gut microbiota.

The type, amount, duration of intervention, study population, and environmental background influence the therapeutic effects.[21,59,60]

In a previous study,[16] the authors used a synbiotic, a mixture of a higher dose (1×10^9) of seven probiotics plus prebiotic fructo-oligosaccharide (FOS) with significant results.

Fifty breastfed infants aged 15–120 days with infantile colic randomly received either the synbiotic sachet (containing 1 billion colony-forming units of *L. casei*, *L. rhamnosus, Streptococcus thermophilus*, *Bifidobacterium breve*, *L. acidophilus*, *B. infantis*, *L. bulgaricus*, and FOS) or placebo daily for 30 days. Reduction in the daily crying time (>50%) was significantly higher in the synbiotic group (82.6%) compared with placebo (35.7%) at

Day 7. At the end of 30 days, treatment success was 87% versus 46% in the synbiotic and the placebo group, respectively.

In 2010, Savino et al.,[61] compared 46 breastfed colicky infants receiving probiotic *L. reuteri* with placebo. Infants of the *L. reuteri*-treated-group showed significantly lower crying on Day 7, 14, and 21. This study suggested that gut microbiota modification made by *L. reuteri* may be involved in the improvement of colicky symptoms.

Other researchers argue that exclusively or predominantly breastfed colicky infants profit from *L. reuteri* DSM 17938 compared with placebo.[62] Saavedra et al.[17] revealed that a formula containing two strains of probiotic (*B. lactis* and *S. thermophiles*) reduced the irritability of colic. A review article[63] supports the positive effects of probiotic supplementation in infantile colic treatment. *L. reuteri* (American Type Culture Collection Strain 55730 and DSM 17938) notably decreased the rate (minutes per day) of crying and pain; additionally, no short-term side effects were identified. On the other hand, a number of trials failed to show the benefit of probiotics in colicky infants.[64] In a review of three studies using synbiotic formula (consisting of *B. longum* and *B. animalis* plus a combination of galacto and FOS) in infancy, synbiotics were shown to have no effect on incidence and frequency of colic restlessness.[65] Altogether, *L. reuteri* DSM 17938, *L. casei*, *L. rhamnosus*, *L. bulgaricus*, *L. acidophilus*, *S. thermophilus*, *B. breve*, *B. infantis*, and FOS are the most effective probiotic formulations being used for the treatment of infantile colic.[66] The trials included in this study have been summarised in Table 1.

Probiotics as a Potential Preventive Intervention for Infantile Colic

A study showed that early life probiotic administration could prevent the onset of GI functional symptoms.[67] The mechanism of action of probiotics in this field has not been determined but appears to be mediated by activity on colonic intrinsic sensory neurons with an improvement in gut motility, as well as having positive effects on function and visceral pain.[68] Probiotics such as *Bifidobacteria* showed *in vitro* anti-inflammatory properties and the ability to inhibit coliform growth, which has a significant presence in colicky infants, and some probiotics exert a direct action on the bacterial growth through bacteriocins production and final fermentation products, inhibiting pathogens, or feeding commensals.[69]

To determine whether excessive crying in infants is preventable by probiotic administration, Pärtty et al.[70] randomised 94 preterm infants, breast and formula-fed, with birth weights >1,500 g and gestational ages of 32–36 weeks, in a double-blind study. From their first 3 days of life they received a mixture of galacto-oligosaccharide and polydextrose (prebiotic group), *L. rhamnosus* GG (probiotic group), or placebo, for 2 months. Follow-up meetings were arranged at the age of 1, 2, 4, 6, and 12 months. Compared with the placebo group, both the prebiotic and probiotic groups displayed less frequent crying (19% versus 19% versus 47%, respectively; p=0.02). The infants' faecal microbiota investigation at 1 month of age shows that the percentage of *Lactobacillus–Lactococcus–Enterococcus* bacteria (14.5% versus 10.5%; p=0.005) and *Clostridium histolyticum* (13.2% versus 10.4%; p=0.11) was greater in excessive criers than in content infants across all three study groups.

The authors showed that early administration probiotics in infants provided relief to their crying and fussing. Based on this study, delayed cloning by *B. infantis* can constitute a risk factor for increasing irritability in preterm infants.[70]

A 2014 RCT performed in 589 breast and formula-fed infants found that the daily administration of *L. reuteri* DSM 17938 from Day 3 for 90 days resulted in a significant reduction in crying time (almost 51 min per day at 1 month, 33 min per day at 3 months).[71] Another RCT that involved both breast and formula-fed infants showed that prophylactic use of *L. reuteri* DSM 17938 during the first 3 months of life reduced the magnitude of crying and functional gastrointestinal disorders.[72]

CONCLUSION

Probiotics supplementation, especially *L. reuteri*, seems to be safe and effective in the management of infantile colic-related pain and fussiness without causing notable side effects.

In the deficit of other efficacious treatment modalities, their roles are valuable. Recent studies showed potential benefits of probiotics for prevention of colic. Higher quality and multicentre RCT with longer follow-up, well-defined outcome measures, and various probiotic and prebiotic mixtures are needed to identify the most effective product in the prevention and treatment of infant colic.

References

1. Savino F. Focus on infantile colic. Acta Paediatrica. 2007;96(9):1259-64.
2. Roberts et al. Infantile colic. Am Fam Physician. 2004;70(4):735-40.
3. Wake M et al. Prevalence, stability, and outcomes of cry-fuss and sleep problems in the first 2 years of life: Prospective community-based study. Pediatrics. 2006;117(3):836-42.
4. Barr RG, "Excessive crying," Sameroff AJ et al. (eds.), Handbook of Developmental Psychopathology (2000), New York: Springer, pp.327-50.
5. Savino F et al. Looking for new treatments of infantile colic. Ital J Pediatr. 2014;40:53.
6. Savino F et al. Infantile colic: Looking to old data through new eyes. Journal of Pediatric and Neonatal Individualized Medicine (JPNIM). 2015;4(2):e040230.
7. Cohen-Silver J, Ratnapalan S. Management of infantile colic: A review. Clin Pediatr. 2009;48(1):14-7.
8. Garrison MM, Christakis DA. A systematic review of treatments for infant colic. Pediatrics. 2000;106(Suppl 1):184-90.
9. Lucassen PL, Assendelft W. Systematic review of treatments for infant colic. Pediatrics. 2001;108(4):1047-8.
10. Adlerberth I, Wold AE. Establishment of the gut microbiota in Western infants. Acta paediatrica. 2009;98(2):229-38.
11. Sung V et al. Treating infant colic with the probiotic Lactobacillus reuteri: Double blind, placebo controlled randomised trial. BMJ. 2014;348:g2107.
12. Savino F et al. Reduction of crying episodes owing to infantile colic: A randomized controlled study on the efficacy of a new infant formula. E J Clin Nutr. 2006;60(11):1304-10.
13. Heine RG. Cow's-milk allergy and lactose malabsorption in infants with colic. J Pediatr Gastroenterol Nutr. 2013;57:S25-S7.
14. Ghosh S, Barr R. "Colic and gas", Pediatric gastrointestinal disease (4th ed) Hamilton, Ont: BC Decker Inc. 2004:210-24.
15. Savino F et al. Ghrelin and motilin concentration in colicky infants. Acta Paediatrica. 2006;95(6):738-41.
16. Kianifar H et et al. Synbiotic in the management of infantile colic: A randomised controlled trial. J Paediatr Child Health. 2014;50(10):801-5.
17. Saavedra JM et al. Long-term consumption of infant formulas containing live probiotic bacteria: Tolerance and safety. Am J Clin Nutr. 2004;79(2):261-7.
18. McMahon C et al. Postnatal depression, anxiety and unsettled infant behaviour. Aust N Z J Psychiatry. 2001;35(5):581-8.
19. Howard CR et al. Parental responses to infant crying and colic: The effect on breastfeeding duration. Breastfeed Med. 2006;1(3):146-55.
20. Barr RG. Preventing abusive head trauma resulting from a failure of normal interaction between infants and their caregivers. Proc Natl Acad Sci U S A. 2012;109(Suppl 2): 17294-301.
21. Ahanchian H et al. Respiratory viral infections in children with asthma: Do they matter and can we prevent them? BMC Pediatr. 2012;12(1):147.
22. Bottazzi V, Reed G. "Other fermented dairy products", Biotechnology: Volume 5, Food and feed production with microorganisms. 1983:315-63.
23. Food and Agriculture Organization of the United Nations, World Health Organization, "Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria", Probiotics in Food: Health and Nutritional Properties and Guidelines for Evaluation (2001). Available at: http://www.fao.org/3/a-a0512e.pdf. Last accessed: 30 October 2018.
24. Gibson GR et al. Dietary modulation of the human colonic microbiota: Updating the concept of prebiotics. Nutr Res Rev. 2004;17(02):259-75.
25. Barnes D, Yeh AM. Bugs and guts practical applications of probiotics for gastrointestinal disorders in children. Nutr Clin Pract. 2015;30(6):747-59.
26. Van den Nieuwboer M et al. Probiotic and synbiotic safety in infants under two years of age. 2014;5(1):45-60.
27. Johnston BC et al. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Cochrane Database Syst Rev. 2011;11(11).
28. Allen SJ et al. Probiotics for treating acute infectious diarrhoea. Cochrane Database Syst Rev. 2010;(11):CD003048.
29. Van den Nieuwboer M et al. Safety of probiotics and synbiotics in children under 18 years of age. Benef Microbes. 2015;6(5):615-30.
30. Enache-Angoulvant A, Hennequin C. Invasive Saccharomyces infection: A comprehensive review. Clin Infec Dis. 2005;41(11):1559-68.
31. Amaral F et al. Commensal microbiota is fundamental for the development of inflammatory pain. Proc Natl Acad Sci USA. 2008;105(6):2193-7.
32. Gill SR et al. Metagenomic analysis of the human distal gut microbiome. Science. 2006;312(5778):1355-9.
33. Turnbaugh PJ et al. The human microbiome project: Exploring the microbial part of ourselves in a changing world. Nature. 2007;449(7164):804.
34. Heijtz RD et al. Normal gut microbiota modulates brain development and behavior. Proc Natl Acad Sci U S A. 2011;108(7):3047-52.
35. Neufeld K-AM et al. Effects of intestinal microbiota on anxiety-like behavior. Commun Integr Biol. 2011;4(4):492-4.
36. Eckburg PB et al. Diversity of the human intestinal microbial flora. Science. 2005;308(5728):1635-8.
37. Qin J et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature. 2010;464(7285):59-65.
38. Bennet R et al. The fecal microflora of 1–3-month-old infants during treatment with eight oral antibiotics. Infection. 2002;30(3):158-60.
39. Cho I et al. Antibiotics in early life alter the murine colonic microbiome and adiposity. Nature. 2012;488(7413):621-6.
40. Karlsson CL et al. The microbiota of the gut in preschool children with normal and excessive body weight. Obesity. 2012;20(11):2257-61.
41. Mayer EA. Gut feelings: The emerging biology of gut–brain communication. Nat Rev Neurosci. 2011;12(8):453-66.

42. Carabotti M et al. The gut-brain axis: Interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol. 2015;28(2):203.
43. Cryan JF, Dinan TG. Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci. 2012;13(10):701-12.
44. Park A et al. Altered colonic function and microbiota profile in a mouse model of chronic depression. Neurogastroenterol Motil. 2013;25(9):733-e575.
45. Holzer P et al. Neuropeptide Y, peptide YY and pancreatic polypeptide in the gut–brain axis. Neuropeptides. 2012;46(6):261-74.
46. Collins SM et al. The interplay between the intestinal microbiota and the brain. Nat Rev Microbiol. 2012;10(11):735-42.
47. Holzer P, Farzi A. Neuropeptides and the microbiota-gut-brain axis. Adv Exp Med Biol. 2014;817:195-219.
48. Bercik P et al. The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. Gastroenterol. 2011;141(2):599-609.e3.
49. Mayer EA et al. Gut/brain axis and the microbiota. J Clin Invest. 2015;125(3):926.
50. Collins SM et al. The adoptive transfer of behavioral phenotype via the intestinal microbiota: Experimental evidence and clinical implications. Curr Opin Microbiol. 2013;16(3):240-5.
51. Sudo N et al. Postnatal microbial colonization programs the hypothalamic–pituitary–adrenal system for stress response in mice. J Physiol. 2004;558(1):263-75.
52. de Weerth C et al. Crying in infants: On the possible role of intestinal microbiota in the development of colic. Gut Microbes. 2013;4(5):416-21.
53. Lehtonen L et al. Intestinal microflora in colicky and noncolicky infants: Bacterial cultures and gas-liquid chromatography. J Ped Gastroenterol Nutr. 1994;19(3):310-4.
54. Savino F et al. Bacterial counts of intestinal Lactobacillus species in infants with colic. Pediatr Allergy Immunol. 2005;16(1):72-5.
55. Savino F et al. Molecular identification of coliform bacteria from colicky breastfed infants. Acta Paediatrica. 2009;98(10):1582-8.
56. Savino F et al. Intestinal microflora in breastfed colicky and non-colicky infants. Acta paediatrica. 2004;93(6):825-9.
57. Pärtty A et al. Compositional development of Bifidobacterium and Lactobacillus microbiota is linked with crying and fussing in early infancy. PloS One. 2012;7(3):e32495.
58. Roos S et al. 454 pyrosequencing analysis on faecal samples from a randomized DBPC trial of colicky infants treated with Lactobacillus reuteri DSM 17938. PLoS One. 2013;8(2):e56710.
59. Kianifar HR et al. Probiotics in the treatment of acute diarrhea in young children. Iran J Med Sci. 2015;34(3):204-7.
60. Heydarian F et al. A comparison between traditional yogurt and probiotic yogurt in non-inflammatory acute gastroenteritis. Saudi Med J. 2010;31(3):280-3.
61. Savino F et al. Lactobacillus reuteri DSM 17938 in infantile colic: A randomized, double-blind, placebo-controlled trial. Pediatrics. 2010;126(3):e526-e33.
62. Szajewska H et al. Lactobacillus reuteri DSM 17938 for the management of infantile colic in breastfed infants: A randomized, double-blind, placebo-controlled trial. J Pediatr. 2013;162(2):257-62.
63. Anabrees J et al. Probiotics for infantile colic: A systematic review. BMC pediatrics. 2013;13(1):1.
64. Ben X-M et al. Low level of galacto-oligosaccharide in infant formula stimulates growth of intestinal Bifidobacteria and Lactobacilli. World J Gastroenterol. 2008;14(42):6564-8.
65. Mugambi MN et al. Synbiotics, probiotics or prebiotics in infant formula for full term infants: A systematic review. Nutr J. 2012;11(1):1.
66. Tintore M et al. Gut microbiota dysbiosis and role of probiotics in infant colic. 2017;8(4):56.
67. Indrio F et al. Prophylactic use of a probiotic in the prevention of colic, regurgitation, and functional constipation: A randomized clinical trial. JAMA Pediatr. 2014;168(3): 228-33.
68. Guandalini S et al. VSL#3 improves symptoms in children with irritable bowel syndrome: A multicenter, randomized, placebo-controlled, double-blind, crossover study. J Pediatr Gastroenterol Nutr. 2010;51(1):24-30.
69. Sanders ME. Impact of probiotics on colonizing microbiota of the gut. J Clin Gastroenterol. 2011;45 Suppl:S115-9.
70. Pärtty A et al. Effects of early prebiotic and probiotic supplementation on development of gut microbiota and fussing and crying in preterm infants: A randomized, double-blind, placebo-controlled trial. J Pediatr. 2013;163(5):1272-7. e2.
71. Indrio F et al. Prophylactic use of a probiotic in the prevention of colic, regurgitation, and functional constipation: A randomized clinical trial. JAMA Pediatr. 2014;168(3): 228-33.
72. Chumpitazi BP et al. Creation and initial evaluation of a Stool Form Scale for children. 2010;157(4):594-7.