STRESA, November 8-10, 2018

VENUE: REGINA PALACE HOTEL

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LUdeS University, United Campus of Malta
Associate Professor of Gastroenterology,
University of Nantes, France
Honorary Clinical Professor,
Chinese University of Hong Kong
Adjunct Professor of Clinical Pharmacology,
University of Parma, Italy

Governor for Italy, *American College of Gastroenterology (ACG)*
General Secretary, *World Organization for Esophageal Diseases (OESO)*

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Anna Bertelé, *MD*

Laboratory for Digestive Pathophysiology
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Ángel Lanas *(Zaragoza, Spain)*
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Eammon M.M. Quigley *(Houston, TX, USA)*
Massimo Rugge *(Padua, Italy)*
Carmelo Scarpignato *(San Ġiljan, Malta)*
Neil H. Stollman *(Oakland, CA, USA)*
Nimish Vakil *(Milwaukee, WI, USA)*
Dino Vaira *(Bologna, Italy)*

STRESA, November 8-10, 2018

VENUE: REGINA PALACE HOTEL

POST-GRADUATE COURSE
in conjunction with the ACG Joint Meeting

THURSDAY, November 8, 2018 – Afternoon

THE WHY, WHEN AND HOW IN GI CLINICAL PHARMACOLOGY

Chairman: Corrado Blandizzi, *MD, PhD (Pisa, Italy)*

13:30	Antisecretory Drugs Richard H. Hunt, *MB BS, FRCP, FRCPC, AGAF, MACG, MWGO (Hamilton, ON, CA)*
14:00	Mucosal Protective Compounds Mario Guslandi, *MD, FACG (Milan, Italy)*
14:30	Prokinetic Agents Carmelo Scarpignato, *MD, DSc, PharmD, FRCP, FACP, FCP, FACG (San Ġiljan, Malta)*
15:00	Laxatives and Colonic Secretagogues Eammon M.M. Quigley, *MD, FRCP, FACP, FACG, FRCPI (Houston, TX, USA)*
15:30	*Questions & Answers*
16:00	*Coffee Break*
16:30	Antidiarrheal Drugs Giovanni Barbara, *MD, FRCP, FACG (Bologna, Italy)*
17:00	Drugs for Visceral Pain Michael Camilleri, *MD, MPhil, MRCP, FACP, FACG, AGAF (Rochester, MI, USA)*
17:30	Antiinflammatory Drugs Jimmy K. Limdi, *MBBS, FRCP (Lond & Ed), FEBGH, FACN, FACG (Manchester, UK)*
18:00	Complementary and Alternative Medicines Pali Hungin, *MD, FRCGP, FRCP, FRSA (Durham, UK)*
18:30	*Questions & Answers*

FRIDAY, November 9, 2018 – Morning

OPENING CEREMONY

09:00 Welcome Address

SESSION I: ESOPHAGUS AND STOMACH

Chairman: Dino Vaira, *MD, PhD, FACG (Bologna, Italy)*

09:30 Non-peptic Esophagitis
Ronnie Fass, *MD, FACP, FACG (Cleveland, HO, USA)*

10:00 Chicago Classification of Achalasia and Other Esophageal Motility Disorders: Impact on Prognosis and Treatment
C. Prakash Gyawali, *MD, MRCP, AGAF, FACG (St. Louis, MI, USA)*

10:30 Management of Gastro-esophageal Reflux Disease: Beyond Acid Suppression
Carmelo Scarpignato, *MD, DSc, PharmD, FRCP, FACP, FCP, FACG (San Ġiljan, Malta)*

11:00 *Coffee Break*

11:30 Gastroparesis and Other Motility Disorders
Michael Camilleri, *MD, MPhil, MRCP, FACP, FACG, AGAF (Rochester, MI, USA)*

12:00 The Way Forward Gastric Cancer: *Helicobacter pylori* Infection and Gastritis
Massimo Rugge, *MD, FACG (Padua, Italy)*

12:30 UGIB: Management in the Era of Novel Antithrombotic Therapies
Guido Costamagna, *MD, FACG (Rome, Italy)*

13:00 *Working Lunch*

FRIDAY, November 9, 2018 – Afternoon

SESSION II: SMALL AND LANGE BOWEL

Chairman: Jimmy K. Limdi, *MB BS, FRCP (Lond & Ed), FEBGH, FACN, FACG (Manchester, UK)*

15:00 Diagnosis and Management of Small Intestine Bacterial Overgrowth
Luigi Gatta, *MD, PhD, FACG (Lido di Camaiore, Italy)*

15:30 Gluten Intolerance and Hypersensitivity: Beyond the Gluten Free Diet
Sheila E. Crowe, *MD, FACP, AGAF, FRCP (San Diego, CA, USA)*

16:00 NSAID-enteropathy: Diagnosis, Prevention and Treatment
Ángel Lanas, *MD, DSc, FACG, AGAF (Zaragoza, Spain)*

16:30 *Coffee Break*

17:00 Pathophysiology and Therapy of Functional Bowel Disorders
Focus on Irritable Bowel Syndrome
Giovanni Barbara, *MD, FRCP, FACG (Bologna, Italy)*

17:30 Diverticular Disease and Its Complications: from Guidelines to Clinical Practice
Neil H. Stollman, *MD, AGAF, FACP, FACG (Oakland, CA, USA)*

18:00 Management of IBD: What the Future Holds
Stephen B. Hanauer, *MD, FACG, AGAF (Chicago, IL, USA)*

SATURDAY, November 10, 2018 – Morning

SESSION III: GUT MICROBIOTA

Chairman: Peter B. Ernst, *DVM, PhD (San Diego, CA, USA)*

09:00 Esophageal and Gastric Microbiome in Health and Disease
Richard H. Hunt, *MB ChB, FRCP, FRCPC, AGAF, MACG, MWGO (Hamilton, ON, CA)*

09:30 Alterations of Gut Microbiome: Implications for the Clinician
Eammon M.M. Quigley, *MD, FRCP, FRCPI, FACP, MACG (Houston, TX, USA)*

10:00 Diet and Drug Induced Dysbiosis
Nimish Vakil, *MD, FACP, AGAF, FASGE, FACG (Milwaukee, WI, USA)*

10:30 *Coffee Break*

11:00 Influence of *Helicobacter* Infection and Its Eradication on Gut Microbiota
Colm O'Morain, *MD, Msc, MRCPI, DSc, FRCPI, MRIA, FRCP, FEBGH, FACG (Dublin, Ireland)*

11:30 Microbiota-directed Therapies in Digestive Disease
Focus on Probiotics and Chronic Intestinal Disorders
Mario Guslandi, *MD, FACG (Milan, Italy)*

12:00 Fecal Microbiota Transplantation: Beyond *C. difficile* Infection
David Armstrong, *MA, MB BChir, FRCPC, FRCP(UK), AGAF, FACG (Hamilton, ON, CA)*

12:30 *Closing Remarks*
Carmelo Scarpignato, *MD, DSc, PharmD, FRCP, FACP, FCP, FACG (San Ġiljan, Malta)*

13:00 *Working Lunch*


CURRENT AND FUTURE
MANAGEMENT OF DIGESTIVE
DISEASE: FROM BENCH TO BEDSIDE

Notes

THURSDAY, November 8, 2018 – Afternoon

POST-GRADUATE COURSE: THE WHY, WHEN AND HOW IN GI CLINICAL PHARMACOLOGY

CHAIRED BY:


Corrado Blandizzi

Corrado Blandizzi, MD, PhD
Professor of Pharmacology & Chairman,
Department of Experimental
& Clinical Medicine,
University of Pisa, Italy


CURRENT AND FUTURE
MANAGEMENT OF DIGESTIVE
DISEASE: FROM BENCH TO BEDSIDE

Notes

STRESA, November 8-10, 2018

VENUE: REGINA PALACE HOTEL

POST-GRADUATE COURSE
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THURSDAY, November 8, 2018 – Afternoon

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CURRENT AND FUTURE
MANAGEMENT OF DIGESTIVE
DISEASE: FROM BENCH TO BEDSIDE

Notes

FRIDAY, November 9, 2018 – Morning

SESSION I:
ESOPHAGUS AND STOMACH

CHAIRED BY:


Dino Vaira

Dino Vaira, MD, PhD, FACG
Professor of Internal Medicine,
University of Bologna, Italy


CURRENT AND FUTURE
MANAGEMENT OF DIGESTIVE
DISEASE: FROM BENCH TO BEDSIDE

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FRIDAY, November 9, 2018 – Morning

SESSION I: ESOPHAGUS AND STOMACH

Chairman: Dino Vaira, *MD, PhD, FACG (Bologna, Italy)*

09:30 Non-peptic Esophagitis
Ronnie Fass, *MD, FACP, FACG (Cleveland, HO, USA)*

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13:00 *Working Lunch*


Ronnie Fass

09:30 Non-peptic Esophagitis

Ronnie Fass, MD, FACP, FACG

Professor of Medicine Case Western Reserve University,
Medical Director, Digestive Health Center,
Director, Division of Gastroenterology and Hepatology
Head, Esophageal and Swallowing Center,
MetroHealth Medical Center, Cleveland, Ohio, USA

Esophageal Injury

Amongst the numerous mechanisms that can lead to esophageal damage, pill induced injury is likely the most common, affecting many patients, who take a long list of medications that can lead to esophageal mucosa damage. Other disorders include, caustic injury, acid- and alkali-induced injury and radiation esophagitis. AIDS presents an opportunity for various infections to lead to esophageal injury in the context of the immune compromised patient.

Pill-induced Injury

Current estimates suggest that more than 70 drugs are capable of causing injury to the esophageal mucosa [1]. Drugs that are commonly associated with pill-induced injury include potassium chloride tablets, tetracycline, doxycycline, quinidine, vitamin C, and alendronate [2]. The injury to the esophageal mucosa may vary from an acute self-limited ulceration to refractory stricture and even death. Mechanisms of pill-induced injury include direct irritant effect of the medication, and disruption of the prostaglandin-mediated barrier in the stomach and esophagus as noted with NSAIDs and aspirin. The risk of pill-induced injury increases with age. Other factors that increase the risk for pill-induced injury include multiple medications, esophageal structural and motility abnormalities (i.e. left atrial enlargement, recent thoracic surgery), reduced salivary flow, and increased time in the supine position. Females are more likely to have pill-induced injury than males, in a ratio of 2 to 1. Most patients who develop pill-induced injury have no antecedent esophageal injury. The injury to the mucosa is a function of the effects of the drug on the esophagus and the circumstances under which the drug is taken (e.g., while supine or/and without water).

The common location for pill-induced injury is in the proximal esophagus (at the level of the aortic arch, approximately 23 cm from the incisors). Patients with left atrial enlargement commonly have pill induced injury at the distal esophagus. Patients typically present with chest pain and odynophagia. Dysphagia, when present, typically reflects inflammatory changes with potential emergence of a stricture. Stricture formation

may occur without prior patient complaints. Strictures are more commonly encountered with quinidine, potassium chloride, and alendronate. See Figure 1 for the endoscopic appearance of pill-induced esophageal injury [3].

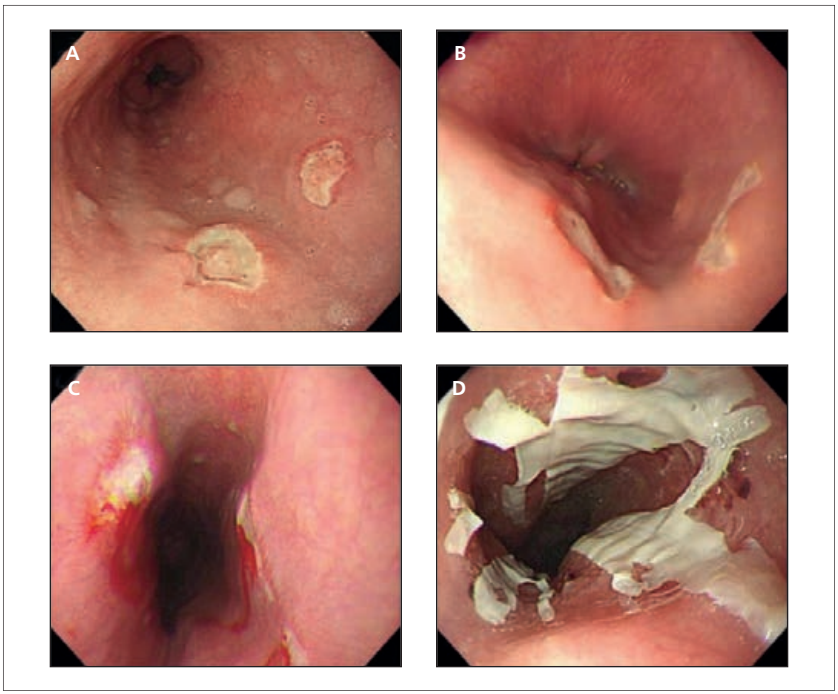

Figure 1: *Endoscopic findings of drug-induced esophagitis;* **A**) *Typical kissing ulcers in the middle third of esophagus;* **B**) *Another typical kissing ulcer;* **C**) *Kissing ulcers with spontaneous bleeding;* **D**) *Coating with drug material (from Kim* et al. *[3])*

Pill-induced injury is often suspected after a careful history. Confirmation of diagnosis can be obtained by endoscopy, which is more sensitive in detecting mucosal changes than radiographic studies. Radiography may be used first if strictures are suspected. Most cases of pill-induced esophagitis will resolve spontaneously within a few weeks. Antacids, H_2-receptor antagonists, proton pump inhibitors, and sucralfate are commonly used, but are of unproven benefit. Management of pill-induced strictures may be difficult, requiring repeated esophageal dilations.

Prevention is best obtained by educating both health care professionals and patients that medications should be taken with at least 150 mL of water (250 mL if using alendronate) prior to and during pill consumption. In addition, prescribing the medication in liquid form can be helpful. The patient should be instructed to take all pills while upright and to remain in this position for at least 15 minutes (30 minutes if using alendronate).

Caustic Injury

Caustic injury is most commonly encountered in the pediatric population, with over half of cases occurring in children <5 years old. These cases are nearly always due to accidental ingestion. In adolescents and adults, caustic ingestion occurs under the influence of drugs, in patients with mental illness, or in those who attempt to commit suicide. Severity and extent of caustic injury to the esophagus is dependent on the following characteristics:

- alkaline *vs* acidic properties of the ingested substance
- the quantity, concentration and composition of the substance (liquid *vs* solid)
- length of time of substance contact with esophageal mucosa.

Of all chemicals that can be ingested, strong alkali and acids are most likely to result in injury, with alkaline materials more likely to affect the esophageal mucosa [4].

Acid Induced Injury

Acids produce coagulative necrosis in the esophagus. They pass rapidly through the esophagus, and the superficial necrosis produced is thought to be protective to the esophageal mucosa. Strong acids are more likely to produce injury to the stomach, although clinically significant esophageal burns may occur in less than half the patients.

Alkali Induced Injury

Alkaline materials include sodium or potassium hydroxide chemicals, detergents, and button batteries. They produce liquefaction necrosis and result in rapid and deep esophageal and gastric injury and usually lasts for three to four days with the development of focal to extensive sloughing and ulceration of the mucosa and later development of granulation tissue and fibrosis over weeks. Full thickness burns are not uncommon. The degree of signs and symptoms does not accurately predict the level of injury. In adults, especially when suicide is the underlying motive, multiple agents should be suspected. Consequently, the clinical presentation may be quite variable, ranging from no symptoms to evidence of mediastinitis, cardiovascular collapse, and death.

Initial management includes assessment of airway patency and breathing. Since the respiratory tract may be involved. Patients should be assessed for hemodynamic instability and, if present, fluids and blood products should be considered. Unstable patients should be managed in the intensive care unit. There is no role for removing the caustic agent by lavage via nasogastric tubes, inducing vomiting or neutralizing

the substance. All these attempts may cause further injury. Thereafter, upper endoscopy should be performed within 12-24 hours. The absence of any signs or symptoms does not exclude severe foregut injury. Endoscopy should be avoided in patients suspected of esophageal perforation.

The subsequent proposed grading system with associated management is a reflection of the degree of esophageal injury and predicted clinical outcomes (Table 1) [5]:

- Grade 0: Normal
- Grade I: Mucosal edema, hyperemia
- Grade II: Ulcers; superficial ulcers, exudates, bleeding (IIA), deep focal ulcers (IIB)
- Grade III: Necrosis; focal (IIIA), extensive (IIIB)

Table 1: Zargar's grading classification of mucosal injury caused by ingestion of caustic substances (from Zargar *et al.* [5])

Grade	Mucosal damage
Grade 0	Normal examination
Grade I	Edema and hyperemia of the mucosa
Grade IIA	Superficial ulceration, erosions, friability, blisters, exudates, hemorrhages, whitish membranes
Grade IIB	Grade IIA plus deep discrete or circumferential ulcerations
Grade IIIA	Small scattered areas of multiple ulceration and areas of necrosis with brown-black or greyish discoloration
Grade IIIB	Extensive necrosis

Grade I and IIA patients have excellent prognosis with little risk of subsequent stricture formation. Patients with greater than Grade IIB injury have more than 70% likelihood of stricture formation, with some patients requiring surgical intervention. The use of corticosteroids aiming to reduce stricture formation is controversial, and is currently not recommended in the setting of advanced grade injury. Broad spectrum antibiotics have been considered a standard of care in patient with Grade III injury and suspicion for esophageal perforation. Proton pump inhibitors may be useful in preventing superimposed GERD, and this may be required for several months until healing has occurred. The timing of esophageal dilation for ingestion associated strictures also remains the subject of disagreement. Some authors recommend initiating dilation with small dilators once the patient is stabilized, hoping to keep the lumen open [4]. Early dilation is generally not recommended due to increased risk of perforation [6].

Most practitioners will wait 3-6 days post ingestion for dilation consideration. Repeated dilation of resistant stricture is a long-term consequence of caustic injury [7].

Radiation Esophagitis

Radiation esophagitis occurs in 50% of patients receiving radiotherapy to the thorax or head and neck region [8]. Radiation suppresses cell proliferation at the basal layer of the epithelium. These cells usually recover in a few days, but repeated radiation will lead to permanent cell damage. Furthermore, radiation can cause thrombosis of blood vessels, leading to ischemia, tissue necrosis, and ulcer formation (Figure 2).

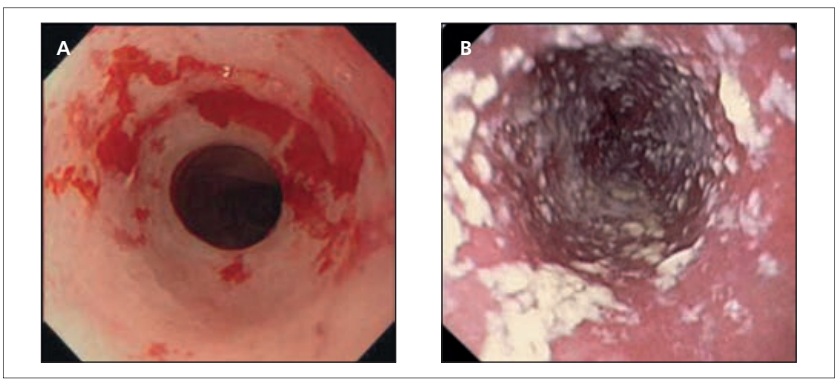

Figure 2: *Endoscopic findings in:* **A**) *Radiation esophagitis with iperemia, erosions and easy touch bleeding;* **B**) *Candida esophagitis with white or slightly yellowish, plaque-like lesions on the esophageal mucosa*

Symptoms of acute radiation-induced injury include chest pain, dysphagia, and odynophagia, which begin to manifest during the second week of radiation exposure. These symptoms can be confused with candida esophagitis, which also commonly occurs as a result of radiation treatment. Chronic radiation induced esophageal injury is associated with inflammation and fibrosis formation within the esophageal musculature and is seen 3 to 6 months after radiation therapy completion. Symptoms and findings of chronic radiation injury include dysphagia related esophageal stricture, esophageal dysmotility, ulceration, trachea-esophageal fistula, and esophageal perforation.

Treatment for acute radiation esophagitis includes supportive measures such as dietary modifications, *viscous* lidocaine, treatment of concomitant candida esophagitis, and nutritional support. The radiation dose should be decreased by 10% or the radiotherapy should be interrupted temporarily. The formation of stricture requires endoscopic dilation or gastrostomy feeding.

Esophageal Injury In the Immunocompromised Patient

Acquired Immune Deficiency Syndrome

In the past, esophageal involvement was commonly encountered in patients with Acquired Immune Deficiency Syndrome *(AIDS)* [9]. In the early days of the disease, many patients presented with Candida esophagitis. The use of highly active antiretroviral treatment (HAART) has resulted in a reduction in the frequency of opportunistic infections in AIDS patients. These infections typically occur when the CD4 count is <200 per mm^3. However, in the era of HAART it is now more common for AIDS patients to complain of esophageal symptoms not specific to AIDS.

Candida still remains the most common cause of esophageal infection in patients with AIDS and those with primary HIV infection, the latter of which is related to the transient immunosuppression occurring with initial infection (Figure 2). Patients complain of symptoms of substernal chest pain with dysphagia. The presence of oral thrush predicts concomitant esophageal candidiasis; however, the absence of thrush does not rule out the presence of esophageal candidiasis. Cytomegalovirus (CMV) has also been associated with esophageal ulcerations with characteristic symptoms of odynophagia and severe substernal chest pain with findings of large deep ulcerations in the esophagus (Figure 3). Herpes simplex (HSV) esophageal ulcerations are associated with diffuse shallow ulcerations in the esophagus (Figure 3). In patients with advanced AIDS with CD4 count <50 mm^3 idiopathic aphthous ulcerations can be encountered in the esophagus with very similar endoscopic findings elated to CMV.

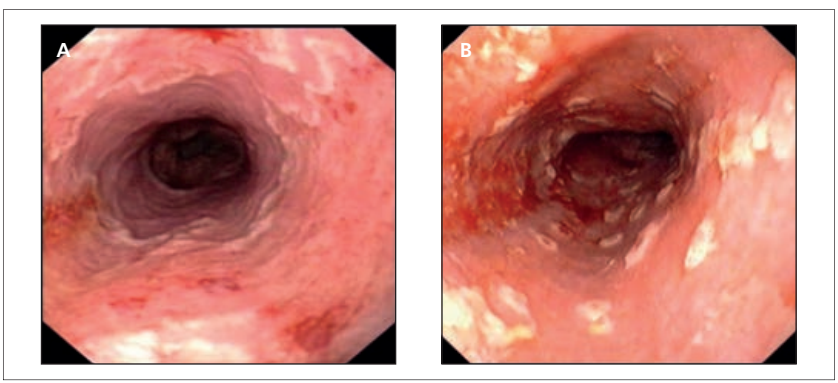

Figure 3: *Endoscopic findings in viral esophagitis:* A) *Cytomegaly virus esophagitis with inflammatory exudates and shallow ulcers in the middle and distal esopaghus;* B) *acute herpes simplex viral esophagitis with inflammatory exudates, ulcerations, and associated granulation tissue in the proximal, middle, and distal portions of the esophagus*

Esophageal ulcerations that are observed on endoscopy require exclusion of Kaposi's sarcoma, lymphoma, squamous cell carcinoma, adenocarcinoma, and pill-induced injury (e.g., zidovudine and zalcitabine).

Endoscopy is key to evaluate symptomatic patients with AIDS and is indicated for those patients who fail to improve with empiric antifungal therapy for esophageal candidiasis. Those suspected of having Candida infection should be treated empirically with fluconazole 100 mg once daily for two weeks after a loading dose of 200 mg. CMV and HSV esophageal ulcers should be treated with specific antiviral agents:

- CMV: ganciclovir 5 mg/kg dose every 12 hours until oral therapy is tolerated for 3-6 weeks,
- HSV: acyclovir 400 mg, five times daily for 14-21 days.

Idiopathic apthous ulcerations respond well to oral steroids with tapering over a period of 4 weeks. Patients, who are not responsive to steroids, can be treated with thalidomide as a second line agent.

Graft versus Host Disease
The esophagus may be affected during the course of bone marrow transplantation. Both chemotherapy and radiotherapy may cause injury to the esophageal mucosa [10]. Additionally, patients are immunocompromised, and thus are more susceptible to various infections. Finally, graft versus host disease (GVHD) may develop. Both acute and chronic forms may occur. In the acute form, all portions of the gastrointestinal tract may be injured, leading to more general gastrointestinal symptoms. Diarrhea is the most common symptom, followed by anorexia, dyspepsia, food intolerance, nausea, and vomiting. Acute esophageal GVHD may present as vesiculobullous, ulcerative, or desquamative lesions. Chronic GVHD may also occur, and if present in the esophagus, it may result in proximal esophageal strictures or webs. Patient may complain of dysphagia, and esophageal dilation may be required.

Eosinophilic Esophagitis

Introduction
Eosinophilic Esophagitis (EoE) was originally described in the pediatric population, but in the last decade has been increasingly recognized in adults. It is a chronic inflammatory process defined by esophageal symptoms, a dense eosinophilic epithelial infiltration (>15 eosinophils/HPF) and the absence of other etiologies causing esophageal eosinophilia. The prevalence of EoE in the United States is estimated to be approximately 57 per 100,000 persons [11]. EoE is an immune mediated disease by which environmental and food antigens stimulate the Th2 inflammatory cascade.

Clinical Presentation

Children present with symptoms of abdominal pain, vomiting, heartburn, and chest pain with associated food impaction that may be related to underlying esophageal stricture or narrowing. Adults on the other hand, more frequently (30-80%) present with food impaction, but most commonly present with dysphagia as well as heartburn, chest pain, nausea, and other symptoms. Interestingly, the degree of mucosal eosinophilia does not correlate with dysphagia severity or symptom improvement with treatment. The degree of dysphagia is more likely related to other factors such as concomitant esophageal dysmotility, degree of mucosal inflammation and fibrostenosis [12].

Diagnosis

The two phenotypes of EoE are defined as the inflammatory and fibrostenotic type (Table 2) [13]. Additional histological features used to support the diagnosis of EoE include eosinophilic degranulation, eosinophilic microabscesses, extension of epithelium into mucosal layers (rete peg elongation), basal zone hyperplasia, spongiosis (intercellular dilation), and fibrosis of the lamina propria. Endoscopic findings may include uniform small caliber esophagus, single or multiple corrugations, esophageal furrows, mucosal abscesses and a stricture (Table 3) [14]. See Figure 4 for a typical endoscopic appearance of eosinophilic esophagitis [15].

Diagnosis is established after biopsies demonstrate dense eosinophilic infiltrate (> 15 eosinophils per high power field). Due to the patchy nature of the eosinophilic infiltrate, two to four biopsies are taken from the distal and proximal esophagus during endoscopy to confirm the diagnosis. Esophageal tear may occur after simple passage of the endoscope, during biopsy, or after dilation. Esophageal manometry findings in EoE include pan-pressurization, which is also seen in achalasia, and increased intrabolus pressure. The role of GERD in EoE remains controversial, and pH testing is not routinely done in these patients, as pH profiles do not predict proton pump inhibitor (PPI) response [16]. Overall, 50-80% if children, and to a lesser extent in adults, have concomitant allergic disease such as allergic rhinitis, asthma, and food allergy. A referral to an immunologist may be prudent in these patients to test for associated allergies, given the complex interplay of these conditions. A positive allergy test for a particular food may identify food as an underlying cause for EoE.

Management

The management goals for EoE include improvement of symptoms, especially dysphagia and fear of food impactions, histological remission of esophageal eosinophilia, endoscopic treatment for eosinophilic inflammation or strictures, and prevention of long-term complications such as strictures, diffuse esophageal narrowing and food impactions [17]. The first step in the treatment of EoE include high dose PPI trial followed by endoscopic assessment of response to therapy including repeat biopsies

Table 2: Criteria for the definition of eosinophilic esophagitis clinical phenotypes (from Atkins *et al.* [13])

Clinical Category	Criteria for Each Category	Method to Assess
Age of Presentation	Infancy Childhood Adult	History
Atopic Status	No evidence of asthma, Allergic rhinitis, Atopic dermatitis or IgE-mediated Food allergy, 1–2 Atopic Conditions 3–4 Atopic Conditions	Immunoassay, skin prick test, history
Natural History of Disease	Fibrostenotic, Food impaction, Resolution	History, Endoscopic, Histologic, Radiologic, Endoflip
Pollen Associated Disease	Yes No	History and endoscopy
Foods eliminated to establish remission	1 Food 2–4 foods >4 foods	History, endoscopy
Responsiveness (clinical and histological) to topical steroids	Traditional dose, High dose CS, Non-responsive to CS	Normalization of histology and symptoms
Molecular Phenotype	TH2 (high TSLP, LTC4), IL23, iNKT (early onset); Mast Cell (high tryptase)	Molecular signature
Stricture Formation	None, Early onset, Late onset	History, radiographic or endoscopic
Familial History of EoE	Yes/No	History, genetic screens
Associated with Immune Deficiency	Frequent infection, known primary immune deficiency (e.g., Dock8)	Genetic analysis
Associated with Collagen Vascular Defects	Marfan-like syndrome	Genetic analysis
Associated with Esophageal Atresia	Esophageal atresia	Genetic analysis, History
Severe Atopic Phenotype: Immune Dysregulation	Associated with severe asthma, atopic dermatitis, multiple IgE mediated food allergies, high peripheral eosinophilia	History

Table 3: Modified classification and grading system for the endoscopic assessment of the esophageal features of eosinophilic esophagitis (from Hirano *et al.* [14])

Major Features	
Fixed rings *(also referred to as concentric rings, corrugated esophagus, corrugated rings, ringed esophagus, trachealisation)*	Grade 0: none Grade 1: mild (subtle circumferential ridges) Grade 2: moderate (distinct rings that do not impair passage of a standard diagnostic adult endoscope (outer diameter 8–9.5 mm)) Grade 3: severe (distinct rings that do not permit passage of a diagnostic endoscope)
Exudates *(also referred to as white spots, plaques)*	Grade 0: none Grade 1: mild (lesions involving <10% of the esophageal surface area) Grade 2: severe (lesions involving >10% of the esophageal surface area)
Furrows *(also referred to as vertical lines, longitudinal furrows)*	Grade 0: absent Grade 1: present
Oedema *(also referred to as decreased vascular markings, mucosal pallor)*	Grade 0: absent (distinct vascularity present) Grade 1: loss of clarity or absence of vascular markings
Stricture	Grade 0: absent Grade 1: present
Minor Features	
Crepe paper esophagus *(mucosal fragility or laceration upon passage of diagnostic endoscope but not after esophageal dilation)*	Grade 0: absent Grade 1: present

to assess eosinophilic infiltrate of the mucosa. This helps to differentiate patients who have gastroesophageal reflux disease (GERD) related eosinophilia, PPI responsive esophageal eosinophilia (PPI-REE) and those with EoE. Patients who have significant drop in eosinophilic infiltrate on PPI therapy, decreased inflammation and symptoms in the absence of objective evidence of GERD, are re-categorized as PPI-REE. In those with EoE, treatments include topical steroids such as aerosolized fluticasone as well as budesonide respules or slurry, twice daily [15,18].

Complications of treatment include oral candidiasis, which occurs in approximately 1% of patients. Both treatments have been shown to decrease eosinophilic infiltrates,

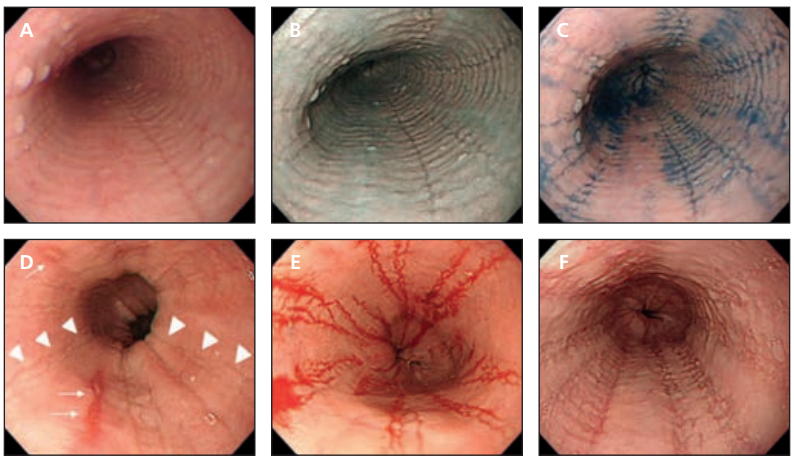

Figure 4: *Endoscopic findings in eosinophilic esophagitis: linear furrows run along the longitudinal axis of the esophagus;* **A**) *White light image;* **B**) *Narrow-band imaging;* **C**) *Indigo carmine-sprayed image;* **D**) *Linear erosion with reflux esophagitis (white arrows) is distinguishable from linear furrows with EoE (while arrow heads);* **E**) *Double line or fissure-like furrows are easily recognized when in contact with blood after esophageal biopsies are obtained;* **F**) *Cobble-stone like appearance is present in the linear furrows in severe cases (from Abe* et al. *[15])*

but with less impressive symptom response. If topical steroids are stopped after initial treatment, most patients will relapse. Thus, maintenance therapy is often required for most patients. Other therapies that have been evaluated in EoE in a few studies include montelukast, a leukotriene inhibitor, azathioprine, IL-5 inhibitors, (mepolizumab and resilizumab), and anti-IgE antibody (omalizamab) [19]. In addition, dietary restrictions have been used in EoE as a long-term treatment modality for patients who can sustain such regimens as elemental diet, six food elimination diet (SFED), and targeted elimination diet. These diets demonstrated varying degrees of successes (40-90% with the highest being in patients taking elemental diets). Lastly, in some patients with a clear fibrostenotic disease, esophageal dilation with either a Savary or Maloney esophageal dilator for symptomatic relief has been recommended.

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C. Prakash Gyawali

10:00 Chicago Classification of Achalasia and Other Esophageal Motility Disorders:Impact on Prognosis and Treatment

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Introduction

The Chicago Classification of esophageal motility disorders was initially developed in response to the paradigm shift in esophageal motor assessment that came with the introduction of esophageal high resolution manometry (HRM) in the early 2000s [1]. In contrast to conventional stacked line tracings, HRM pressure data is acquired digitally from solid state circumferential pressure sensors (1 cm apart), embedded on an esophageal motility catheter. The acquired data is supplemented with best fit computer generated data in between recording sites. Dedicated software programs are used to assimilate and display these data. Specific amplitudes are assigned colors, such that the HRM 'Clouse plot' (named after the esophageal pioneer who developed HRM, Ray Clouse) can be viewed from above, like a weather map [1]. The Clouse plot is anchored by two bands of pressure, the upper esophageal sphincter (UES) and the esophagogastric junction (EGJ), consisting of the lower esophageal sphincter (LES) and the crural diaphragm (CD). Esophageal peristalsis consists of three contracting segments, a proximal skeletal muscle segment in continuity with the UES, and two smooth muscle contraction segments in the distal esophagus, the distal of which seamlessly transitions into the LES. The manometry procedure has become shorter, and esophageal anatomic and physiologic function can be viewed real-time, eliminating the stationary pull-through maneuver, previously utilized for identification of the LES [2].

Software Tools

The introduction of HRM allowed development of software tools to reliably interrogate electronic pressure data. Three software tools are utilized in the interrogation of esophageal motor function (Figure 1). The most intuitive software tool is the ***integrated relaxation pressure*** (IRP), which consists of the nadir pressure over 4 continuous or discontinuous seconds during the period of LES relaxation following a test swallow [3]. An elevated IRP above the upper limit of normal defines esophageal outflow obstruction, which is a cardinal feature of achalasia [4]. Compared to single sensor or sleeve sensor assessments of LES relaxation, IRP has significantly higher sensitivity and specificity in the identification of achalasia [3,5].

Table 1: The Chicago classification of esophageal motility V 3.0
(from Kahrilas *et al.* [4])

Achalasia and EGJ Outflow Obstruction	Criteria
Type I achalasia (classic achalasia)	Elevated median IRP (>15 mmHg†), 100% failed peristalsis
	(DCI <100 mmHg)
	Premature contractions with DCI values less than 450 mmHg·s·cm satisfy criteria for failed peristalsis
Type II achalasia (with esophageal compression)	Elevated median IRP (>15 mmHg†), 100% failed peristalsis, panesophageal pressurization with ≥20% of swallows
	Contractions may be masked by esophageal pressurization and DCI should not be calculated
Type III achalasia (spastic achalasia)	Elevated median IRP (>15 mmHg†), no normal peristalsis, premature (spastic) contractions with DCI >450 mmHg·s·cm with ≥20% of swallows
	May be mixed with panesophageal pressurization
EGJ outflow obstruction	Elevated median IRP (>15 mmHg†), sufficient evidence of peristalsis such that criteria for types I-III achalasia are not met*
Major Disorders of Peristalsis	*(Not encountered in normal subjects)*
Absent contractility	Normal median IRP, 100% failed peristalsis
	Achalasia should be considered when IRP values are borderline and when there is evidence of esophageal pressurization
	Premature contractions with DCI values less than 450 mmHg·s·cm meet criteria for failed peristalsis
Distal esophageal spasm	Normal median IRP, ≥20% premature contractions with DCI >450 mmHg·s·cm†. Some normal peristalsis may be present
	At least two swallows with DCI >8,000 mmHg·s·cm †§
	Hypercontractility may involve, or even be localized to, the LES
Hypercontractile esophagus (Jackhammer)	At least two swallows with DCI >8,000 mmHg·s·cm †§
	Hypercontractility may involve, or even be localized to, the LES
Minor Disorders of Peristalsis	*(Characterized by contractile vigor and contraction pattern)*
Ineffective esophageal motility (IEM)	≥50% ineffective swallows
	Ineffective swallows can be failed or weak (DCI<450 mmHg·s·cm)
	Multiple repetitive swallow assessment may be helpful in determining peristaltic reserve

† Cutoff value dependent on the manometric hardware; this is the cutoff for the Sierra device
* Potential etiologies: early achalasia, mechanical obstruction, esophageal wall stiffness, or manifestation of hiatal hernia
§ Hypercontractile esophagus can be a manifestation of outflow obstruction as evident by instances in which it occurs in association with an IRP greater than the upper limit of normal

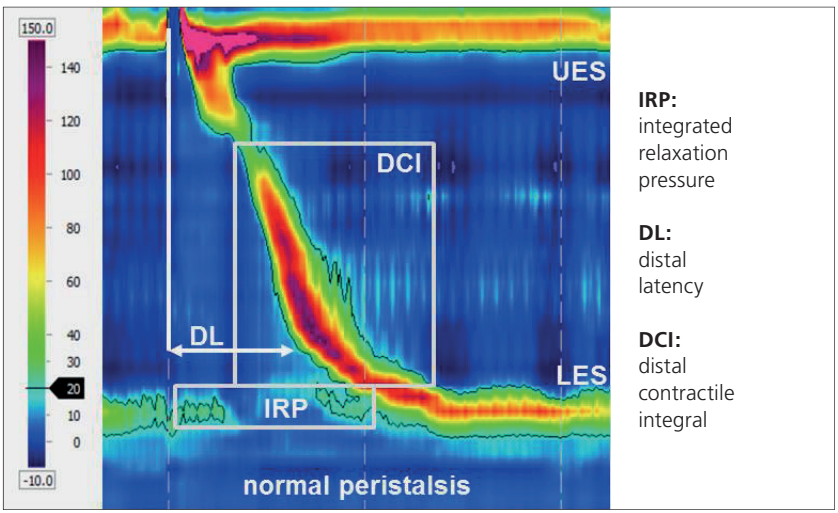

Figure 1: *The three key HR manometry parameters for a precise diagnosis of esophageal motor disorders*

Esophageal body motor function is assessed with two software tools. ***Distal contractile integral*** (DCI) assesses the vigor of esophageal smooth muscle contraction, taking length, duration and amplitude of the contracting segment [6]. ***Distal latency*** (DL) assesses timing of smooth muscle contraction, and measures the time from UES relaxation to the arrival of the contraction segment at the ***contractile deceleration point*** (CDP), where fast esophageal body contraction transitions to the slower emptying phase of peristalsis at the EGJ [7].

Chicago Classification Version 3.0

The current version of the Chicago Classification (version 3.0) categorizes esophageal body motor function on the basis of IRP, DCI and DL (Table 1)[4]. These software tools are used in hierarchical fashion, and the IRP is assessed first. An elevated IRP indicates the presence of esophageal outflow obstruction. The esophageal body motor pattern then allows differentiation of ***achalasia*** into subtypes [8]. ***Type 1*** achalasia has no esophageal body peristalsis, and no pressurization. ***Type 2*** achalasia demonstrates esophageal pressurization, manifest as pan-esophageal increase in intrabolus pressure between the UES and the LES, in at least 20% of swallows. ***Type 3*** achalasia manifests at least 20% premature sequences (DL<4.5 s). EGJ outflow obstruction (EGJOO) is diagnosed if esophageal body motor function is intact in the setting of an elevated IRP [4]. Both motor processes (achalasia-like abnormal LES relaxation) and

structural lesions (tight stricture, infiltrating processes, paraesophageal hernia) can result in EGJOO, and additional testing is typically necessary to make a final diagnosis.

If the IRP is normal, other ***major motor disorders*** are diagnosed based on DCI and DL (Table 1). Hypercontractile esophagus (Jackhammer esophagus) consists of exaggerated esophageal body contraction vigor >8000 mmHg•cm/s in at least 20% of swallows [9]. Distal esophageal spasm (DES) consists of at least 20% premature sequences with intact contraction (DCI>450 mmHg•cm/s) [10]. Both these spastic disorders are not seen in healthy individuals, and can be associated with chest pain and/or dysphagia [4]. Absent contractility is diagnosed when none of the swallows generate esophageal peristalsis, with DCI<100 mmHg•cm/s with all sequences.

Minor motility disorders are not pathognomonic of disease, and can be encountered in healthy asymptomatic controls; functional esophageal disorders can coexist with minor disorders. The most consistent feature of minor disorders is that esophageal bolus transit (and consequently, clearance of refluxate) may be suboptimal [11]. Fragmented peristalsis consists of at least 50% of swallows with >5 cm breaks in esophageal body peristalsis using a 20 mmHg isocontour, but with esophageal body contraction vigor in the intact range (i.e. >450 mmHg•cm/s). Ineffective esophageal motility (IEM) consists at least 50% failed (DCI<100 mmHg•cm/s) and/or weak swallows (DCI 100-450 mmHg•cm/s). Both these minor motility disorders are encountered more often in the setting of gastroesophageal reflux disease compared to healthy controls [12].

Diagnostic Pitfalls

The IRP is a critical metric used in HRM, and therefore it is imperative that normative thresholds are correctly utilized. The upper threshold of normal IRP is derived from the 95th percentile value in asymptomatic adults; consequently, values marginally above the normative threshold could be within normal range. Further, the normal values are specific to the HRM equipment utilized, as each commercial HRM set-up has its own threshold of normal [13]. It is also important to recognize that achalasia remains possible with a normal IRP [14]. Therefore, with compatible symptoms and absent contractility in the esophageal body, alternate testing is necessary with barium radiography or endo-FLIP (Endoluminal Functional Lumen Imaging Probe), especially when IRP is in the high normal range.

Esophageal longitudinal muscle contraction can pull the EGJ proximally into the thoracic cavity, and consequently, the IRP measurement boxes may no longer align with the location of the LES. This will result in a falsely low IRP, from LES pseudo-relaxation. It is important to move the IRP measurement box proximally over the LES when the esophagus shortens in order to accurately capture the IRP [2].

Use of opiate medications can increase the IRP and shorten DL, leading to an erroneous diagnosis of idiopathic type 3 achalasia or EGJOO [15]. Similarly, the use of

metoclopramide can increase EGJ and LES tone. Smooth muscle relaxants and phosphodiesterase inhibitors can reduce esophageal body contraction vigor. The use of medications needs to be factored into the analysis.

Provocative tests performed during esophageal HRM help further clarify motor diagnoses. The simplest provocative test is multiple rapid swallows (MRS), where five swallows of 2 mL ambient temperature water are administered 3-4 seconds apart [16]. During the swallows, there is profound motor inhibition of the esophageal body and the LES. After the final swallow of the sequence, the LES regains its tone, and the esophageal body manifests an augmented contraction sequence, termed contraction reserve. Abnormal inhibition (as seen in the achalasia spectrum disorders and hypercontractile disorders) will result in contraction segments during the repetitive swallows. Abnormal contraction will manifest lack of augmentation of contraction following MRS when compared to contraction vigor from single swallows. The presence of ***contraction reserve*** in minor motor disorders (fragmented peristalsis, IEM) indicates that a standard fundoplication can be performed if needed in the context of reflux disease, and that the likelihood of persistence or future development of IEM is lower [16,17].

Rapid drink challenge (RDC) is another provocative test that is useful to determine if there is a ***latent*** obstructive process at the EGJ, when a standard 10 swallow protocol does not identify esophageal outflow obstruction [18]. The patient is asked to drink 100-200 mL of water rapidly with the catheter in place. Similar to MRS, there is profound motor inhibition during the swallows; however, the presence of a contraction sequence is not consistently observed following RDC. Instead, the presence of compartmentalization of intrabolus pressure during the swallows or an elevated trans-EGJ pressure gradient indicate the likelihood of an obstructive process [19,20]. Solid test meals may provide similar information, but are more cumbersome and time-consuming to perform [21].

Management of Motility Disorders

Achalasia spectrum disorders are the most important diagnoses that are made with esophageal HRM, as successful and durable management can be offered (Figure 2) [22,23]. Type 2 achalasia results in the best treatment outcome, where any form of disruption of the EGJ results in durable symptom relief. Both pneumatic dilation and myotomy (laparoscopic myotomy, per oral endoscopic myotomy) can reliably improve symptoms in type 2 achalasia. While outcome is typically not as successful as with type 2 achalasia, type 1 achalasia also responds to both pneumatic dilation and myotomy, but may respond to myotomy better than pneumatic dilation. Therefore, institutional expertise and availability of either procedure can direct the individual management approach. If the initial management approach fails, the alternate approach can be offered to the patient.

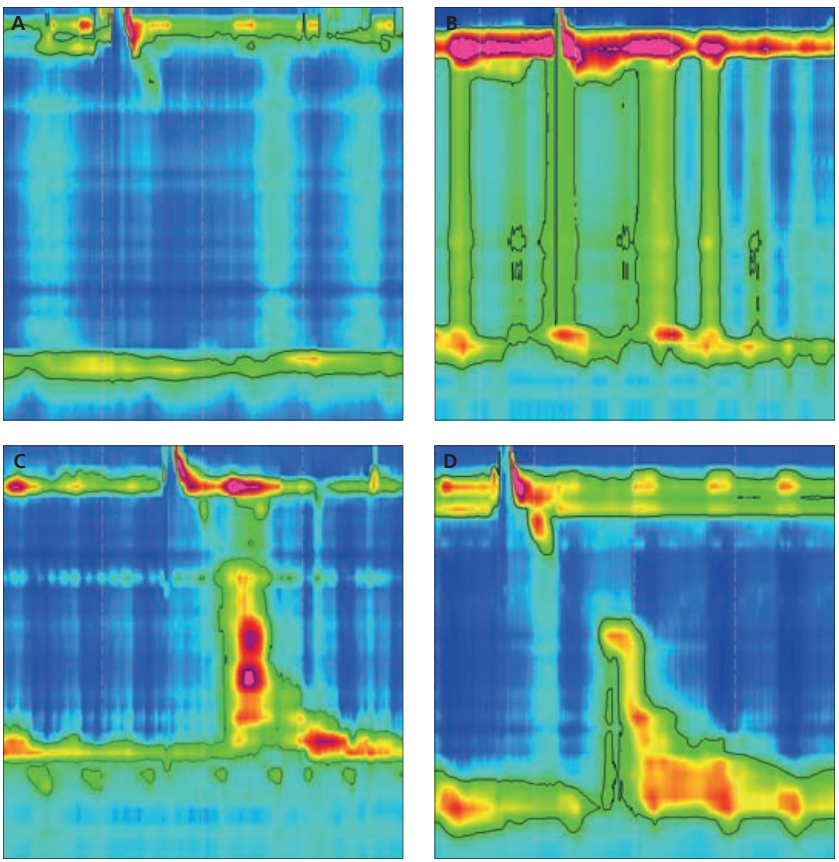

Figure 2: *High-resolution manometry of achalasia subtypes.* **A**) *According to the Chicago Classification v3.0, the criteria for classic achalasia (type I achalasia) are an integrated relaxation pressure (IRP) ≥15 mmHg and absent peristalsis without marked pressurization or contractions.* **B**) *Achalasia with esophageal pressurization (type II achalasia) has an IRP ≥15 mmHg and at least 20% of swallows associated with pan-esophageal pressurization to >30 mmHg.* **C**) *Spastic achalasia (type III achalasia) has an IRP ≥15 mmHg and a spastic contraction with ≥20% of test swallows 20.* **D**) *An example of esophagogastric junction (EGJ) outflow obstruction treated as achalasia but not meeting diagnostic criteria for achalasia because of preserved fragments of peristalsis. Dashed white lines represent initial upper oesophageal sphincter relaxation DL, distal latency (from Kahrilas* et al. *[22])*

Patients who are considered poor candidates for invasive management (e.g. elderly patients, patients with significant cardiorespiratory comorbidities, patients on chronic anticoagulation) can be offered botulinum toxin (BTX) injection into the LES, which can provide symptom benefit in two-thirds of patients, with benefits lasting several months to several years at a time. Repeat injections can be performed when symptoms recur [22,23].

Type 3 achalasia does not respond as well as types 1 and 2 achalasia to pneumatic dilation or laparoscopic myotomy, since the esophageal body smooth muscle, which contracts prematurely and sometimes aggressively (spasm) also needs to be disrupted. Type 3 achalasia may be a niche indication for per oral endoscopic myotomy (POEM), where disruption of the esophageal body smooth muscle can be performed in conjunction with LES myotomy. A prominent consequence of POEM is reflux disease, which is reported in as many as half of patients on objective testing [24].

EGJOO needs careful additional investigation before specific management is planned, using barium radiography, endoscopic ultrasound, and endo-FLIP (Figure 3) [25], in addition to endoscopy and biopsy.

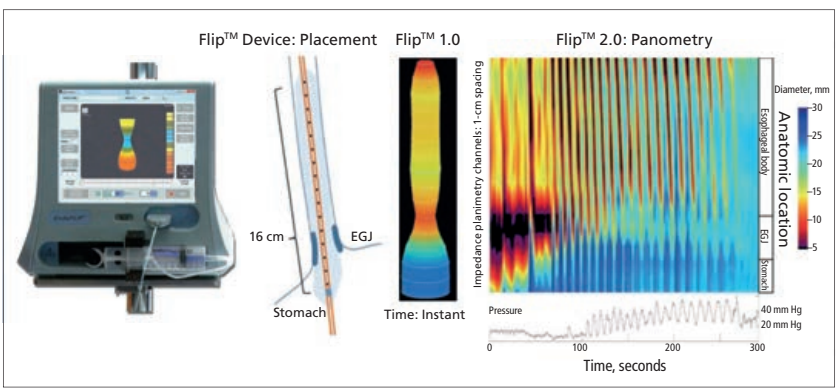

Figure 3: *Flip™ technology and data output using a color scale for diameter. The device is placed through the EGJ with 2 to 3 sensors into the stomach. Flip™ 1.0 provides real-time data on the diameters in a 3-dimensional geometry to illustrate the distensibility of the esophageal wall and EGJ. Contractions can be seen in red on the top of the recording segment in Flip™ 1.0 and the EGJ can be seen as an hourglass configuration. Flip™ 2.0 provides diameter topography similar to high-resolution manometry, and the axial length extends across the EGJ and into the stomach. Contractions are visualized as changes in diameter that move antegrade or retrograde up and down the esophagus. This is an example of normal motility and a normal EGJ opening*

The purpose of additional investigation is to determine the mechanism of esophageal outflow obstruction. If a motor mechanism is suspected, management similar to achalasia can provide benefit [26]. Identified structural abnormalities such as strictures, neoplasia, infiltrating disorders and paraesophageal hernias are managed accordingly.

Smooth muscle relaxants and botulinum toxin injection can be of value in some patients with hypermotility disorders (hypercontractile esophagus and DES), but these approaches are not uniformly effective. Per oral endoscopic myotomy is an option for hypercontractile esophagus, especially if there is a prominent dysphagia component [22].

There is no specific management available for hypomotility disorders. Patients with dysphagia are asked to eat small bites in the upright position, and use fluids to push solids down when necessary. Concurrent reflux disease is treated with acid suppression.

Future Directions

New metrics to assess EGJ barrier function have been recently introduced. The ***EGJ contractile integral*** (CI) is a DCI-like metric that incorporates EGJ basal pressure, variation with respiration and EGJ length [27]. Initial reports indicate that a low EGJ-CI is associated with elevated esophageal reflux burden on ambulatory reflux monitoring (Figure 4) [28].

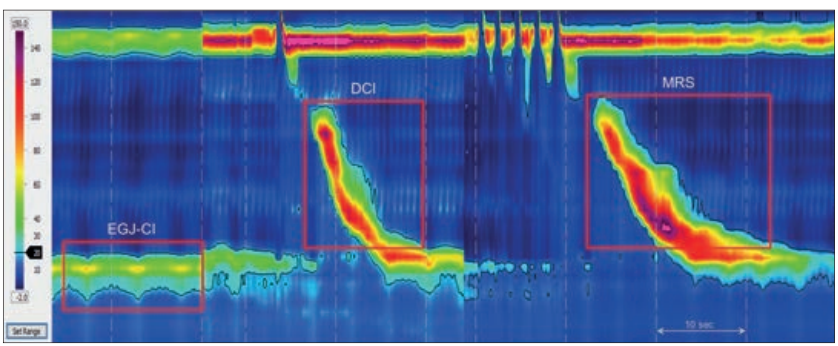

Figure 4: *The esophagogastric junction contractile integral (EGJ-CI), measured during esophageal HRM. The EGJ-CI measures vigour of the EGJ barrier using a software tool that encompasses length and vigour of the EGJ above the gastric baseline. The measurement is made over three respiratory cycles during quiet rest, and corrected for duration of respiration. The distal contractile integral (DCI) measures vigour of smooth muscle contraction taking length, duration and amplitude of contraction into consideration. Following a series of repetitive swallows (multiple rapid swallows (MRS)), DCI augments higher than mean DCI from single swallows when there is contraction reserve (from Gyawali* et al. *[28])*

EGJ morphology can be categorized into three subtypes based on the anatomic relationship between the intrinsic LES and the CD: the two are superimposed in type 1 EGJ; separated by <3 cm in type 2 EGJ, and by ≥3 cm in type 3 EGJ [27]. Hierarchical classification of motor findings in GERD includes evaluation of EGJ morphology and barrier function, esophageal body motor function, and contraction reserve [27]. Relationships between esophageal pressure metrics and esophageal reflux burden on ambulatory reflux monitoring continue to be researched.

When stationary impedance is incorporated into esophageal HRM, bolus transit can be assessed concurrently with pressure topography (Figure 5) [11]. *High resolution impedance manometry* (HRIM) can be of value in demonstrating esophageal bolus retention in achalasia spectrum disorders. Esophageal impedance ***bolus height*** can be assessed after a 200 mL water challenge, and this correlates well with the barium column height on a timed upright barium swallow [29]. ***Bolus flow time*** can be calculated when EGJ pressure declines concurrently with bolus presence on impedance at the EGJ, which may have higher accuracy than IRP in assessing EGJ function following achalasia therapy [30].

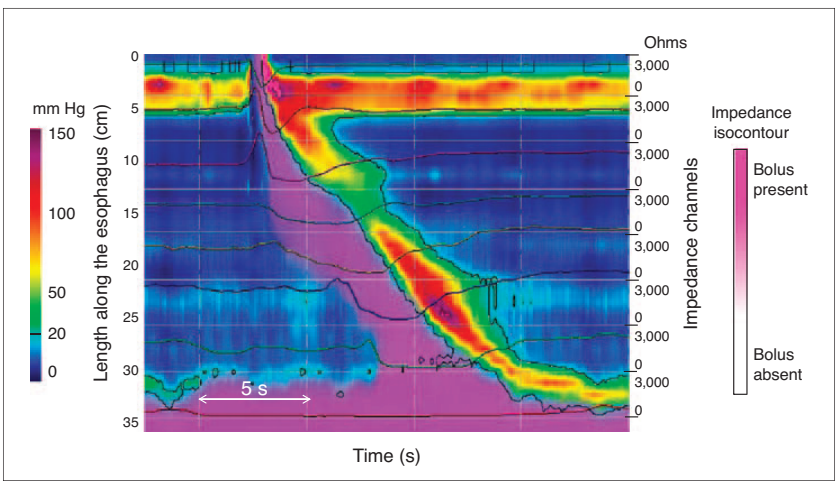

Figure 5: *Example of intact peristalsis associated with complete bolus transit in high-resolution impedance manometry (HRIM) study. Impedance tracings are superimposed to esophageal pressure topography (EPT) and impedance data are also displayed by overlaid pink colorization. The pink shaded area indicates bolus presence. Complete bolus transit was observed with the onset of contraction at each esophageal level corresponding to the clearance of pink colorization and the upward inflection in the impedance tracings (from Roman* et al. *[11])*

Low baseline impedance on HRIM correlates with esophageal reflux burden, similar to baseline impedance on pH-impedance monitoring [31]. The relationship between esophageal bolus presence on HRIM and contractile patterns is being investigated, and new metrics are being devised to quantify bolus presence on impedance plots.

Assessment of EGJ and esophageal body distensibility using *endo-FLIP* can augment manometric evaluation of EGJ function. EGJ distensibility index is low in the setting of esophageal outflow obstruction and achalasia [32]. Distinct esophageal body contractile patterns are recognized in the presence of esophageal outflow obstruction, which may facilitate diagnosis of achalasia spectrum disorders without need for manometry [32,33].

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Carmelo Scarpignato

10:30 Management of Gastroesophageal Reflux Disease: Beyond Acid Suppression

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Gastro-esophageal reflux (i.e. the reflux of gastric contents into the esophagus, GER) is a physiological phenomenon, occurring in everybody, especially after large and fat meals. Under physiologic conditions, efficient esophageal clearing mechanisms return most of the refluxed material to the stomach and symptoms do not occur [1]. However, when the reflux of gastric contents is large or aggressive enough, it causes symptoms and/or complications and impairs quality of life, giving rise to GER disease (GERD) [2]. According to the Montreal definition [3], GERD is a chronic condition which develops when the reflux of stomach contents causes troublesome and recurrent symptoms (which could be typical, i.e. esophageal or/and atypical, i.e. extra-esophageal), and/or complications, which include esophagitis, ulcer, stricture and Barrett's esophagus.

GERD is a highly prevalent disorder in Western Europe, North and South America, as its predominant symptom, heartburn, can occur once a week in up to 26% of the general population [4]. Despite geographical variations, the prevalence of GERD is increasing worldwide.

Over the past decade, it has been realized that there are two different phenotypes of the disease. Some patients present with esophageal mucosal lesions (i.e. erosive esophagitis), but the majority (up to 70%) have a macroscopically normal mucosa at endoscopy. Such patients are usually considered to have non-erosive reflux disease (NERD) [3,5].

Medical Management of GERD

Symptoms are crucial to the diagnosis of typical GERD and represent the main therapeutic target. Despite the symptom pattern does not allow to differentiate the erosive disease from NERD [6], patients seek medical assistance because of symptoms and ask for quick symptom relief.

The *aims of GERD therapy* are therefore the following [7,8]:

- Symptom relief, with consequent improvement of quality of life
- Healing of esophageal lesions
- Prevention of recurrences (both symptomatic and endoscopic) and of complications

GERD is primarily a motor disorder and its pathogenesis is *multifactorial* (Figure 1) [9]. The main motility abnormalities include an impaired function of the lower esophageal sphincter (LES), an abnormal esophageal clearance, and a delayed gastric emptying in up to 40% of cases. The presence of hiatal hernia favors reflux, but this association is not mandatory. The ultimate consequence of the above motor abnormalities is the presence of acid in the wrong place (i.e. in contact with the esophageal mucosa) [10]. In addition, the amount of reflux increases markedly after meals both in healthy subjects and GERD patients, an event almost exclusively due to the increase of transient (inappropriate) LES relaxations by meal-induced gastric accommodation.

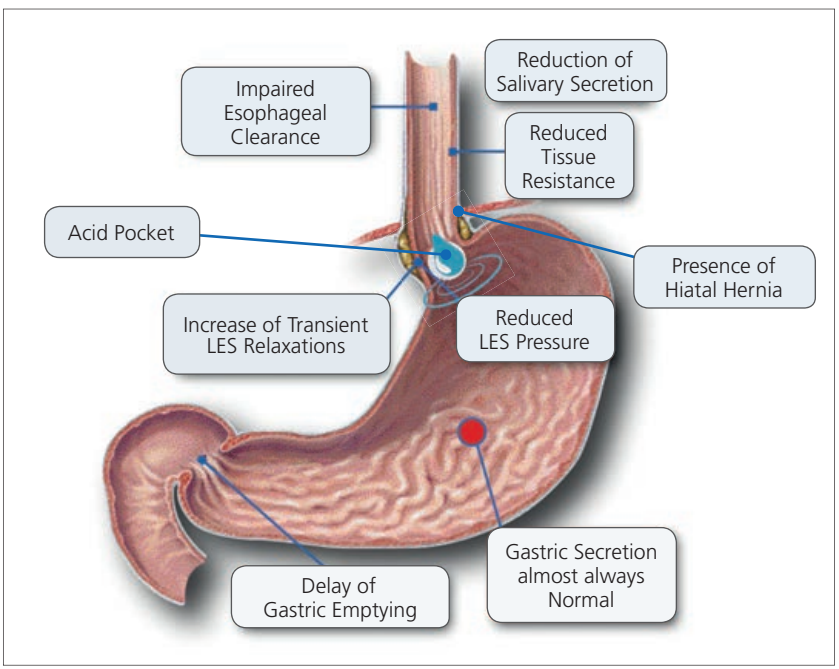


Figure 1: *Pathophysiology of GERD (modified from Savarino & Scarpignato [9])*

Despite the buffering content of food, the pH of the material refluxed into the distal esophagus is very acidic due to the presence of an "acid pocket", which occurs in both healthy subjects and GERD patients. It represents an area of unbuffered gastric acid that accumulates in the proximal stomach after meals and serves as a reservoir for acid reflux [11]. The abnormal esophageal exposure to acid, on the other hand, is not secondary to gastric acid hypersecretion, which has been documented only in a small subset of GERD patients [10]. All the above pathophysiological mechanisms are exaggerated in obese subjects [12,13].

Current pharmacologic approaches to address this clinically challenging condition are limited. Reflux inhibitors represent a promise unfulfilled, effective prokinetics are lacking and antidepressants, despite being effective in selected patients , give rise to adverse events in up to 32% of patients [14-17]. Antisecretory drugs (H_2-receptor antagonists, H_2RAs, and proton pump inhibitors, PPIs) remain therefore the mainstay of medical treatment for GERD. They act indirectly by reducing the amount and concentration of gastric secretion available for reflux, thus lessening the aggressive power of the refluxed material [7,18]. PPIs also reduce the size of the acid pocket and increase the pH (from 1 to 4) of its content [11]. The clinical efficacy of these drugs has been clearly shown in many studies and the superiority of PPIs over H_2RAs has been established beyond doubt [19]. The greater pharmacodynamic effect of PPIs depends on their ability to block the final step in the production of acid, regardless the secretory stimulus. Moreover, PPIs are relatively more effective during the daytime than the night-time and this leads to a better control of post-prandial reflux events [19].

Efficacy of PPIs in GERD

Eight-week therapy with standard (once daily) dose PPIs can achieve healing of reflux esophagitis in more than 80% of patients [20], a rate depending on the severity of mucosal lesions [21,22]. This healing rate can be further improved by doubling the PPI dose (NNT=25) [20]. Meta-analyses have shown that – when compared to omeprazole, lansoprazole and pantoprazole – esomeprazole achieves the highest healing rates of reflux esophagitis in the short-term [21-23]. The more favorable clinical benefit of esomeprazole appears negligible in less severe esophagitis (A & B according to the Los Angeles classification [24,25]), but it might be important in more severe disease [22]. Vonoprazan, a member of the new generation *reversible* PPIs (called potassium-competitive acid blockers, P-CABs), is able to achieve higher intragastric pH, effectively controlling both daytime and night-time acid secretion [26]. As a consequence, it proved to be capable of healing almost 100% of severe (C & D) esophagitis [27], a benefit also maintained during the remission phase [28].

PPIs are effective in obtaining symptom relief in both erosive and non-erosive disease [29]. Their efficacy for the relief of regurgitation is however modest, and considerably lower than that achieved for heartburn [30]. The myth that PPIs are less effective in

NERD has been dispelled by a meta-analysis [31], showing that – when a functional investigation (pH-metry or pH-impedance-recording) is added to a negative endoscopy to objectively confirm this condition – the estimated complete symptom response rate after PPI therapy is comparable to that observed in patients with erosive disease.

NERD is however an umbrella term, including at least 4 different patient subgroups [32], of whom only those where acid is implicated in symptom generation (i.e. true NERD and patients with acid hypersensitive esophagus) are clearly responsive to PPIs (Figure 2) [33]. This is not the case of patients who are hypersensitive to nonacidic reflux or those with functional heartburn. According to Rome IV criteria [34], both acid hypersensitive esophagus (now called *reflux hypersensitivity*) and functional heartburn are functional GI disorders, which should no longer be included in GERD. The lack of abnormal acid exposure and symptom-reflux association makes patients with functional heartburn not responsive to PPIs. This subgroup of subjects may benefit of visceral analgesics (e.g. antidepressants) [16].

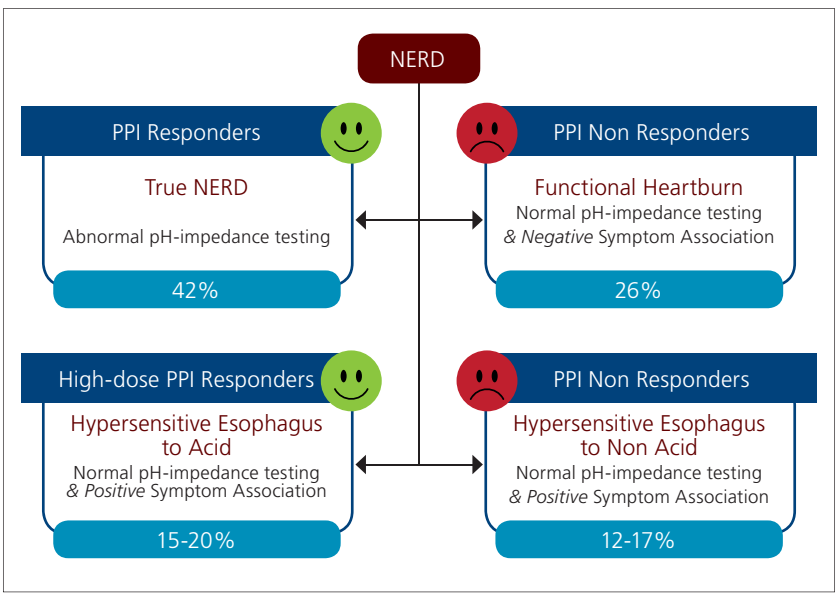


Figure 2: *Subgroups of NERD patients and their response to PPIs: lessons from pH-impedance Monitoring (from Scarpignato [33])*

Although not as frequent as previously suggested, PPI-refractory heartburn, occurring more commonly in NERD than in erosive disease, does exist however. Some 20% (range 15-27%) of correctly diagnosed and *appropriately* treated patients do not respond to PPI therapy at standard doses [35,36]. On multivariate analysis, the presence of irritable bowel syndrome, epigastric pain and post-prandial distress episodes were associated with poor response to PPI therapy [36]. To ascertain whether they are "truly" PPI-resistant, compliance and adherence to treatment should be checked. Indeed, PPIs are often taken inappropriately, with only 27% of GERD patients dosing their PPI correctly and only 12% dosing it optimally in a USA survey [37]. Although a standard PPI dose can occasionally control symptoms, nocturnal intragastric acidity often remains elevated (with Nocturnal Acid Breakthrough, NAB) in these patients. A split regimen (either standard or double dose) of PPIs b.i.d. (before breakfast and before evening meal) provides superior acid control. In patients with persistent nocturnal symptoms, the addition of an H_2RA at bedtime may be indicated to control NAB and associated esophageal acidification [33,38-40], despite the likely development of tolerance to H_2RA [41]. The majority of patients, however, reported persistent improvement in GERD symptoms from night-time H_2RA use [39]. To reduce the development of tolerance, on demand or cyclic dosing may be preferable, but this approach has not been specifically studied.

PPIs for Maintenance of GERD

GERD and NERD are chronic, relapsing diseases. Six months after cessation of treatment, symptomatic relapse is rapid and frequent (i.e. in 90% of endoscopy-positive and 75% of endoscopy-negative patients [6]). PPIs, both at a full and half dose, are able to maintain patients in remission, with a superior efficacy of the full dose (NNT=9.1) [42]. Esomeprazole 20 mg is the only step-down dose PPI able to maintain in symptomatic remission a significantly higher proportion of GERD patients compared to lansoprazole 15 mg [23,43] or pantoprazole 20 mg [23].

Since PPIs do not correct the underlying pathophysiological motor abnormalities responsible for GERD, a continuous treatment is required to maintain all patients in remission. In the LOTUS trial [44], comparing long-term esomeprazole therapy with anti-reflux surgery (ARS), the estimated remission rate at 5 years was 92%, higher than that (57%) reported with omeprazole in the SOPRAN study [45]. However, while the PPI dose in the SOPRAN trial was fixed, in the LOTUS investigation, patients whose reflux symptoms were not adequately controlled by a standard maintenance regimen (i.e., esomeprazole, 20 mg/die) were allowed to increase the dosage to 40 mg once daily and then to 20 mg twice daily. This dose titration may have contributed to the improved remission rate and suggests that long-term maintenance therapy should be individualized. Indeed, the number and severity of relapses are highly variable amongst patients. Infrequent reflux symptoms are less likely to be chronic and may respond to different management strategies. There are basically three different long-term

approaches for GERD treatment with PPIs: continuous (i.e. every day), intermittent (i.e. cycles of daily PPI administration) or *on-demand* (i.e. symptom-driven) therapy, each selected on the basis of patients' clinical characteristics [46].

One third of patients, submitted to fundoplication, is reported to take acid-lowering compounds (mostly PPIs) after anti-reflux surgery, but only few studies have specified whether drug use was on a regular or occasional basis [47]. A meta-analysis of RCTs [48] found that – after anti-reflux surgery – 14% of patients still require antisecretory drugs. This figure increases with the duration of follow-up and up to one third of patients required antisecretory drugs after 10 years. The data from non-randomized studies [49], which are higher than the estimation provided by randomized studies (i.e. 20% of patients under acid suppression), are probably more representative of the current clinical practice.

A recent consensus paper [50] recommended invasive therapy (i.e. laparoscopic fundoplication or magnetic sphincter augmentation) for the treatment of PPI unresponsive symptoms in *proven* GERD *only* in the presence of abnormal reflux burden, with or without hiatal hernia, or regurgitation with positive symptom-reflux association and a large hiatus hernia, while non-invasive pharmacologic or behavioral therapies were considered preferable for all other scenarios.

PPIs for Extra-digestive GERD

Conversely from typical symptoms, the efficacy of PPIs on extra-esophageal manifestations of GERD is uncertain. This uncertainty could result, at least in part, from the available studies, which are not homogeneous, with differences in patient selection, end-point considered, drug used and regimen adopted. In addition, since extra-digestive symptoms may need higher PPI dose and clinical improvement may take a longer time to occur, only properly designed trials would be able to unravel a clinical response. Unfortunately, however, this has not always been the case.

A careful analysis of the available literature clearly shows that the efficacy of PPIs in extra-digestive GERD is less consistent than that observed in patients with typical symptoms. A synopsis of effectiveness and failure of PPIs in extra-esophageal manifestation of GERD is shown in Figure 3.

The efficacy of PPIs in non-cardiac chest pain (NCCP) and extra-digestive GERD is disappointing. In these clinical conditions, PPIs are usually given twice daily and for extended periods (i.e. 3 or more months). However, evidence is often lacking and, where available, not strong enough to allow clear recommendations to be made.

GERD being the most common and best-studied cause of NCCP, acid suppression is the initial pharmacological approach in this patient population. A systematic review

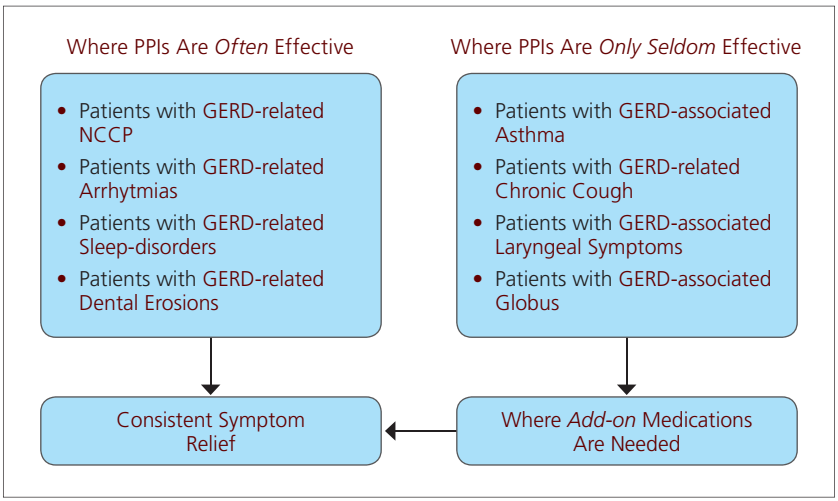


Figure 3: *Effectiveness and failure of acid suppression in extra-digestive GERD*

showed that patients with endoscopic or pH-monitoring evidence of GERD tend to improve, but not resolve, with PPI therapy, whereas GERD-negative patients display little or no response [30], a result confirmed by a more recent meta-analysis [51]. PPIs might also improve symptoms related to atrial fibrillation and other supraventricular arrhythmias, especially after meal, in patients with proven GERD [52].

Despite the negative conclusions of a Cochrane meta-analysis [53], a more recent review [54] suggests that a therapeutic benefit for acid-suppressive therapy in patients with chronic cough cannot be dismissed, advocating a rigorous patient selection that could allow the identification of patient subgroups likely to be responsive. On the contrary, no systematic reviews and meta-analyses [55-60] found any significant clinical benefit of PPI therapy over placebo in reflux laryngitis.

Asthma and GERD can often coexist, with reflux disease being reported in 40% to 80% of patients with asthma. While asthma medications can trigger GERD [61,62], PPIs might on the contrary improve asthma control. Here again, an early Cochrane review [63] showed no benefit of PPI therapy on nocturnal symptom score and lung function, but a recent meta-analysis [53] – by selecting the morning peak expiratory flow (PEF) rate as primary outcome – disclosed a benefit of PPIs over placebo, which was greater in patients with proven GERD.

Despite the widespread use of PPIs in dental practice to manage the oral manifestations of GERD [64], treatment of dental erosions represents the only *objectively* documented clinical use [65].

In extra-digestive GERD, the complexity of patient presentation is matched only by the challenge in making an appropriate diagnosis of reflux as the cause for the patients' complaints. Upper GI endoscopy and pH-impedance monitoring suffer from poor sensitivity while laryngoscopy suffers from poor specificity in diagnosing reflux in this group of patients [66,67]. An empiric trial of PPIs could be the initial approach to diagnose and treat the potential underlying cause of these extra-digestive symptoms [67]. Symptom resolution usually needs higher PPI dose and longer treatment time than those adopted in patients with typical GERD [67,68]. However, it is important to highlight that PPI therapy in extra-digestive GERD and twice daily dosing are both unapproved indications for these agents but one that is recommended by both GI [69, 70] and other specialty guidelines [71-73].

An Alternative Approach to GERD Esophageal Mucosal Protection

As already pointed out, gastro-esophageal reflux is a physiological phenomenon, occurring in everybody, which remains asymptomatic thanks to efficient esophageal clearing mechanisms [1]. However, the integrity of esophageal mucosa as well as the its mechanisms of defense play also a pivotal role [74]. These mechanisms can be classified in: pre-epithelial (i.e. salivary secretion, mucus and bicarbonate secretion), epithelial (the stratified squamous epithelium, which limits the hydrogen ion back diffusion and buffers them) and post-epithelial (mainly mucosal blood flow, which provides bicarbonate ions for H^+ neutralization, also favoring the cellular repair mechanisms) [74].

Several studies have shown that, in patients with GERD, pre-epithelial defense mechanisms are impaired. Salivary secretion [75] and pharyngeal swallowing [76] are significantly decreased, likely reducing the esophageal clearance, especially during night-time, when most esophageal defense mechanisms are lessened by the supine position [77]. A more recent investigation has also shown that salivary secretion of both bicarbonate and epidermal growth factor (EGF) is significantly reduced in patients with Barrett's esophagus [78]. The functional changes may contribute to the development of esophageal lesions, where subsequently mucus-secreting columnar cells replace reflux-damaged esophageal squamous cells, giving the so-call Barrett's metaplasia [79].

Dilation of intercellular spaces (DIS), the hallmark of damaged esophageal epithelium [80-82], correlates well with trans-epithelial resistance [83] and the low basal esophageal impedance in patients with both erosive and non-erosive reflux disease [83] mirrors an impairment of esophageal mucosal integrity in these patients [84]. Despite this, stimulation of esophageal defense mechanisms and/or esophageal mucosal protection have only seldom been attempted as therapeutic approach to GERD.

An ideal therapy for GERD patients should – in addition to acid secretion – fully address pathophysiology of the disease, providing a barrier to (and/or bind) the residual aggressive components of the refluxate (i.e. weakly acidic content and pepsin) while stimulating mucosal repair.

Esophageal clearance can be improved by stimulating salivary secretion with ***chewing-gum*** [85, 86], an effect shared by some ***prokinetic compounds***, like cisapride [87-89] and tegaserod [90], which unfortunately have been withdrawn from the market [91].

Antisecretory drugs can also help to re-establish, albeit *indirectly*, esophageal mucosal integrity. By using esophageal potential difference (PD) as an index of mucosal integrity, it was shown that treatment of patients with erosive esophagitis with high dose (40 mg twice daily) famotidine normalizes PD values [92]. In addition, 4-week treatment with omeprazole (20 mg daily) of patients with NERD prevents acid-induced changes in PD [93]. Along the same lines, long-term treatment with PPIs is followed by reduction of DIS in both erosive and non-erosive GERD [94,95]. It must be pointed out that both H_2RAs and PPIs do possess some non-antisecretory activities (like, for instance, stimulation of salivary secretion by nizatidine [89] or increase of mucus production by rabeprazole [96]), which might contribute the above-observed clinical effects.

The first drug that was shown to be capable of protecting the human esophageal epithelium against acid injury is ***sucralfate***. Orlando and Tobey in the 90's reported that sucrose octasulfate (SOS), one of sucralfate major components, is able to prevent the TER drop induced by acid perfusion in human esophageal biopsies *in vitro* [97]. Since SOS is devoid of any antacid or buffering activity, its effect was attributed to a direct stimulation of esophageal defense mechanisms, strengthening mucosal integrity. Although sucralfate has been used in the past for the treatment of reflux esophagitis [98], it was abandoned after the advent of acid suppression, especially with PPIs. The lack of an adequate formulation, able to remain long in contact with the esophageal mucosa, has likely contributed to lessen interest on its esophago-protective activity. Transit time of liquids through the esophagus is indeed very short (less than 16 sec), even in a supine subject [99]. A viscous liquid formulation that adheres to and coat the mucosa will limit the contact of refluxed acid and pepsin with the epithelial surface [100] and can act as a vehicle to deliver drugs for local action within the esophagus [101].

Alginate-containing formulations, of which the most widely used and studied is ***Gaviscon®***, have long been considered as a mechanical barrier to reflux [102]. However, recent developments in GERD pathophysiology allowed a reappraisal of their pharmacological properties, which include their selective localization in the acid pocket [11] and their binding activity of pepsin and bile acids [103]. A recent study, performed on human esophageal biopsies from patients with GERD, showed that pre-treatment

with alginate formulation was able to prevent the drop of TER induced by a noxious solution, including acid, pepsin and bile [104]. Subsequent studies in esophageal cell cultures have confirmed these results and demonstrated that fluorescein-labeled alginate solutions adhere to the esophageal mucosa, where they persist for at least 1 hour [105].

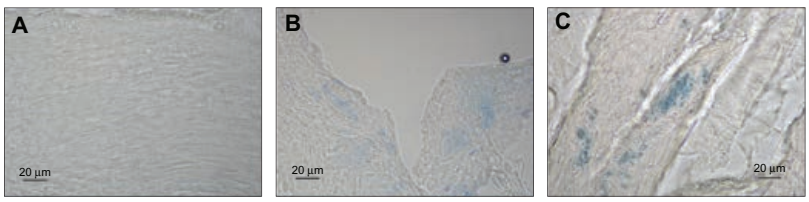
Over the past year, a class III medical device was specifically designed by and developed by APharm (Arona, NO, Italy) and marketed in many Countries under the brand name ***Esoxx***® (by Alfasigma SpA, Bologna, Italy) or ***Ziverel***® (Norgine, Harefield, Uxbridge, UK). It consists of a mixture (1:2.5 ratio) of low molecular weight (80-100 KDa) hyaluronic acid and low molecular weight (10-20 KDa) chondroitin sulphate, dispersed in a bioadhesive carrier (poloxamer 407) to form a macromolecular complex, coating the esophageal mucosa and acting as a mechanical barrier against the noxious components of the refluxate [106].

The components of this medical device are two well-known physiologic substances. ***Hyaluronic acid*** is a widespread, biologically active substance, which regulates cellular function through interaction with specific receptor. It is a multifunctional, high molecular weight glycosaminoglycan, component of the majority of extracellular matrices and involved in several key physiologic processes, including wound repair and regeneration, morphogenesis and matrix organization [107]. Topic hyaluronic acid formulations are employed to treat recurrent aphthous ulceration of the oral mucosa with fast symptom relief [108], to which the dose-dependent anti-inflammatory activity of the compound may also contribute [109]. ***Chondroitin sulphate*** is a natural glycosaminoglycan, present in the extracellular matrix surrounding cells, especially in the cartilage, skin, blood vessels, ligaments and tendons, where it forms an essential component of proteoglycans [110]. Current evidence shows that chondroitin sulphate fulfills important biological functions in inflammation, cell proliferation, differentiation, migration, tissue morphogenesis, organogenesis, infection and wound repair. The compound is endowed with immune-modulatory, anti-inflammatory and antioxidant properties [111]. Along with non-specific interactions, chondroitin sulphate may display specific binding to bioactive molecules, such as pepsin. Peptic activity is indeed reduced both *in vitro* [112] and *in vivo* [113,114] and treatment of peptic ulcer with chondroitin sulphate has been attempted in the past [115].

Poloxamer 407 (ethylene oxide and propylene oxide blocks) is a hydrophilic non-ionic surfactant, which shows thermo-reversible properties of the utmost interest in optimizing drug formulation (fluid state at room temperature, facilitating administration and gel state above sol-gel transition temperature at body temperature, promoting prolonged release of pharmacological agents) [116]. Poloxamer 407 formulations lead to enhanced solubilization of poorly water-soluble drugs and prolonged release profile for many galenic applications. The poloxamer 407 adhesive properties are used to

lengthen residence time of agents in the gastro-intestinal tract [116]. Good adhesion in the esophagus with efficient diffusion of the drug into the mucosa was observed in the mouse, by means of an optical fiber spectrofluorimetric method [117].

An *ex-vivo* experimental study on a swine model showed that perfusion of the esophageal lumen with this medical device is able to prevent the increase in mucosal permeability induced by acid and/or pepsin (Figure 4) [118].



No Damage [No Stain] Mild Damage [Weak Stain] Severe Damage [Strong Stain]

Perfusion of Evans Bleu dye

	No Stain	Weak Stain	Strong Stain
Saline	100%	–	–
Pepsin Solution	–	33%	67%
Pepsin Solution + Esoxx®	100%	–	–
Pepsin Solution + Saline + Esoxx®	100%	–	–

Figure 4: *Perfusion of swine esophageal mucosa with acidified (pH=2) pepsin solution: effect of Esoxx® pretreatment (modified from De Simone* et al. *[118])*

How Effective Is Mucosal Protection in GERD

A recent consensus paper of the Romanian Society of Neurogastroenterology [119] reviewed the available literature (which is scarce and sparse) and – on the basis of current evidence – recommended mucosal protective compounds for the treatment of chronic heartburn, especially in patients with mild reflux symptoms. Due their high efficacy in GERD, it is unlikely that these drugs can be considered a real alternative to

PPIs. Rather, their use as *add-on* medications in both naïve patients and PPI-refractory patients, is advisable [120]. There is indeed increasing evidence suggesting that – in patients with proven digestive or extra-digestive GERD – PPIs alone may not suffice and the use of *add-on* medications can achieve a higher success rate.

In some placebo-controlled trials [121,122], addition of Gaviscon Advance to PPI therapy improved overall *typical* reflux symptoms as well as night-time symptoms compared to antisecreterory therapy alone. Compared to acid suppression alone, the combination of esomeprazole and Gaviscon® Advance attained a significantly better reduction of the reflux symptom index (RSI) in patients with laryngo-pharyngeal reflux (LPR) [123]. The efficacy of alginates in extra-esophageal manifestations of GERD are likely due to its barrier effect, which translates into a reduction of the proximal migration of the refluxed gastric contents [124] and binding and inactivation of pepsin [103]. The concentration and mucosal damaging activity of pepsin are potentially very high in the (acidic or nonacidic) refluxate that can reach the upper airways [125].

Two clinical studies demonstrated that short-term treatment with Esoxx achieves a significant and quick symptom relief both in patients with erosive [126] or non-erosive reflux disease [127]. To provide a rationale for its use as *added-on* medication, a double-blind, placebo-controlled trial evaluated the efficacy of Esoxx®, combined to acid suppression, *versus* acid suppression alone, in patients with NERD, diagnosed merely as *endoscopy-negative reflux disease* [106]. This patient population was selected to mirror the clinical practice, outside the referral centers, where advanced investigations are not available. The *primary endpoint* was the treatment efficacy analysis, which was calculated as the proportion of patients with at least 3-point reduction of the total symptom score (TSS). There were 4 different *secondary endpoints*: **1**) number of patients with 50% reduction of total symptom score at final visit; **2**) number of patients with TSS reduction at the final visit; **3**) TSS change after treatment and **4**) HRQL physical and mental items according to the SF-36 questionnaire. Changes in the severity and frequency of each symptom (heartburn, acid regurgitation, retrosternal pain, acid taste in the mouth) were also evaluated. At the end of treatment, both the primary and secondary endpoints were reached by a significantly higher number of patients with combined therapy (Table 1). The same was true also for HRQL which improved with both treatments, but some items were significantly better after Esoxx® plus PPI therapy. In addition, the combination of acid suppression and mucosal protection was more effective that PPI treatment alone in reducing both the intensity and frequency of each evaluated symptoms (particularly regurgitation) [103]. This finding is very interesting, especially on the light of the limited efficacy of PPIs on this symptom [30].

Table 1: Effect of Esoxx®, combined with PPI therapy, on primary and secondary end-points in patients with NERD: ITT analysis (from Savarino *et al.* [106])

Trial End-points	PPI + Esoxx®		PPI + Placebo		*p value*
	n/N	%	n/N	%	
Primary					
N° of Patients with TSS reduction of at least 3 points	40/76	52.6	25/78	32.1	0.01
Secondary					
N°. of Patients with 50% reduction of TSS	29/76	38.2	18/78	23.1	0.042
N° of Patients with TSS reduction at final visit	60/76	78.9	44/78	56.4	0.003
TSS (±SD) before and after treatment	Before	After	Before	After	
	8.53±2.6	5.42±2.1	8.03±2.7	6.49±2.6	
Change (± SD) in TSS	-3.11±3.1		-1.54±3.0		0.002
TSS = Total Symptom (Heartburn, Retrosternal Pain, Regurgitation, Acid Taste) Score					

The mucosal coating properties of Esoxx® combined with its antipeptic activity let foresee its efficacy in extra-digestive GERD. In this connection, a double-blind trial is ongoing and the results are eagerly awaited.

It is worthwhile emphasizing that alginate-containing formulations and those including the macromolecular complex between poloxamer 407 and hyaluronic acid/ chondroitin sulphate represent two complementary approaches, which are no mutually exclusive. Alginate formulations are *mainly* indicated in the prevention and treatment of post-prandial reflux (thanks to their mechanical effect and localization on the acid pocket) while the medical device (with stimulating properties on mucosal healing and defenses) should be taken away from meals. Their combination is therefore possible (and rationale), provided the different administration timings be respected.

A suggested algorithm for the management of GERD is shown in Figure 5, where anti-reflux surgery is also considered [128]. Fundoplication, which – conversely from drug therapy – is able to address almost all the underlying pathophysiology of GERD (Table 2) [129], could be a reasonable choice in patients with moderate-to-severe reflux and large hiatal hernia as well as regurgitation despite antisecretory or combined therapy, in whom volume reflux may be the cause for patients' continued symptoms.

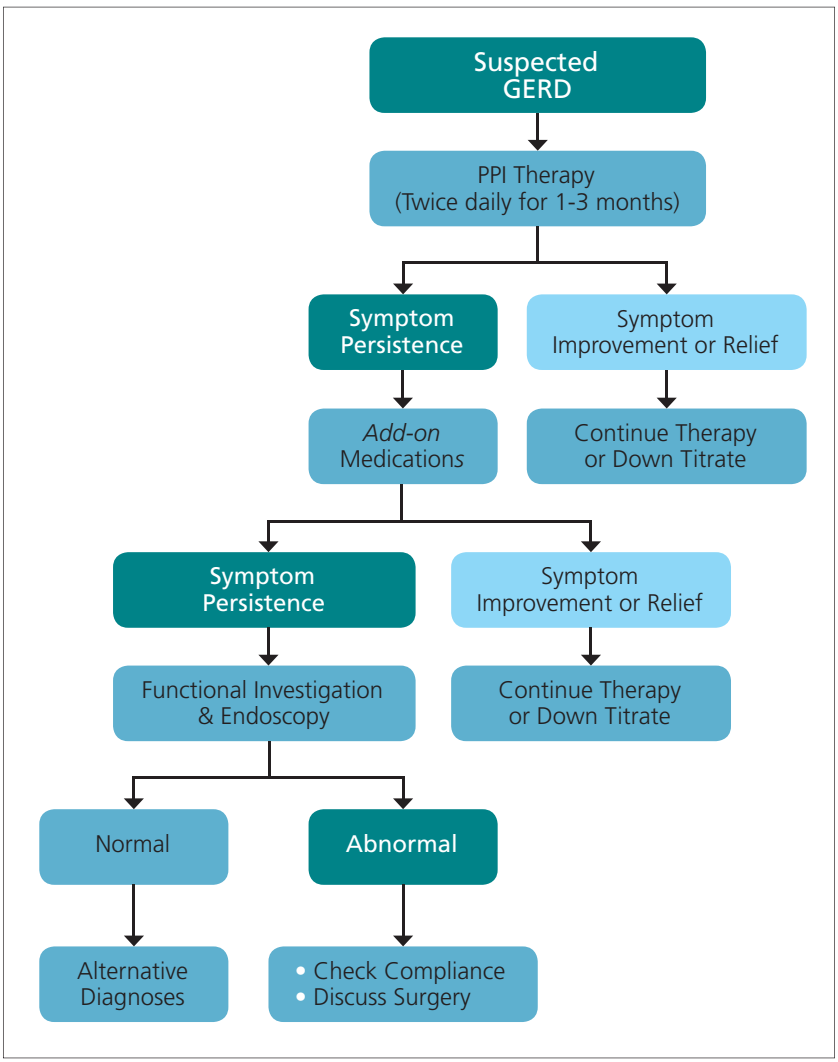


Figure 5: *Suggested flow-chart for the management of GERD (modified from Scarpignato & Gatta [120]*

Table 2: Management of GERD: comparative effects of medical and surgical therapies on the underlying pathophysiology (modified from Contini & Scarpignato [121].

	PPIs	Prokinetic Drugs	Barrier Drugs	Mucosal Protectives	Anti-reflux Surgery
Defective LES	0	++	0	0	+++
Transient LESRs	0	+	0	0	+++
Hiatal Hernia	0	0	0	0	+++
Impaired Clearence	0	+	0	0	+ (?)
Mucosal Resistance	0	0	+	+++	0
Acid-pepsin Injury	+++	+	++	++	+++
DGE Reflux	+	+ (?)	++	++	+++
Gastric Emptying	0(-)	++	0	0	+++

LES: Lower Esophageal Sphinter; LESRs: Lower Esophageal Sphinter Relaxations;
DGE: Duodeno-gastric-esophageal Reflux

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CURRENT AND FUTURE
MANAGEMENT OF DIGESTIVE
DISEASE: FROM BENCH TO BEDSIDE

Notes


Michael Camilleri

11:30 Gastroparesis and Other Motility Disorders

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Introduction
The objective of this review is to discuss what's new in the diagnosis and management of gastroparesis and related disorders. Traditionally, gastroparesis is described as a syndrome characterized by delayed gastric emptying in absence of mechanical obstruction of stomach [1]. However, in recent years, the spectrum has been broadened to "gastroparesis and related disorders" with recommendation to reconsider the definition of gastroparesis, recognizing it as a broader spectrum of gastric neuromuscular dysfunction [2]. The cardinal symptoms include postprandial fullness (early satiety), nausea, vomiting, and bloating. In one tertiary referral series, diabetes mellitus (DM) accounted for almost 1/3 cases of gastroparesis. Indeed, symptoms attributable to gastroparesis are reported by 5 to 12% of patients with diabetes.

Pathophysiology
This spectrum of disorders results form neuromuscular dysfunction. Vagal innervation is essential for gastric accommodation, mediated by intrinsic inhibitory mechanisms such as nitrergic neurons, and antral contractions essential for triturating solid food are mediated by extrinsic vagal innervation and intrinsic cholinergic neurons. Smooth muscle disorders may be infiltrative (as in scleroderma) or degenerative (as in hollow visceral myopathy, amyloidosis, and rarely, mitochondrial cytopathy).

Screening for vagal dysfunction can be achieved by seeking the presence of sinus arrhythmia (normal) on a long duration EKG recording. Myopathic disorders are invariably associated with a component of more generalized motility disorder affecting other regions of the gut, e.g. small bowel, LES and esophagus, and systemic features such as CREST syndrome in scleroderma and external ophthalmoplegia or skeletal muscle involvement in mitochondrial cytopathy.

Etiopathogenesis
The most common conditions associated with gastroparesis are idiopathic, diabetic, iatrogenic post-surgical and post-viral. The commonest surgical association is with fun-

doplication and bariatric procedures; the commonest iatrogenic associations are with μ opioid agonists and hypoglycemic agents such as amylin analogs (e.g. pramlintide) or GLP-1 analogs or agonists (e.g. liraglutide and exenatide) but not dipeptidyl peptidase IV inhibitors (such as vildagliptin and sitagliptin), which increase GLP-1, improves glycemia without delaying gastric emptying [3]. The devastating effects of opioids on gastroparesis are illustrated by the report from Temple University in 223 patients: 70.9% not taking opioids, 9.9% opioids only as needed, 19.3% on chronic scheduled opioids (median morphine equivalent dose 60mg/day) for at least 1 month, and of the latter group, 8.1% were on opioids for gastroparesis and/or stomach pain. The patients on opioids compared to non-opioid controls had higher symptoms severity, lower employment rate, higher hospitalizations in the last 1 year and worse outcomes with treatment with prokinetics agents and gastric electrical stimulation [4,5].

A prodromal viral illness prior to the gastroparesis is generally associated with a good prognosis when patients are followed for ~1 year [6], unless there is virus-induced selective or pan-dysautonomia with Ebstein-Barr virus, citomegalovirus, and herpes virus; this form of gastroparesis in the setting of dysautonomia has a poor prognosis [7].

Symptoms Associated with Gastroparesis and Related Disorders

Clustered Symptoms including Nausea, Vomiting and Postprandial Fullness

The symptoms traditionally associated with gastroparesis typically occur in combination, not as individual symptoms. Thus, the upper GI symptoms of 483 diabetics evaluated from a US National phone interview showed the cardinal symptoms of diabetes occur in clusters e.g. pain with early satiety and heartburn; heartburn with bloating, early satiety, nausea and vomiting; and regurgitation with bloating, nausea and vomiting [8]. The symptoms in idiopathic and diabetic gastroparesis tend to be similar, though vomiting and early satiety are more frequent in diabetic, and pain more frequent in idiopathic gastroparesis [9].

Pain

In the NIH Gastroparesis Consortium patient cohort [10], the predominant symptoms in 393 patients were pain/discomfort in 21% and nausea/vomiting in 44%. Pain was rated moderate or severe in 66% of those with pain. Idiopathic gastroparesis (256 patients) was correlated with opioid and antiemetic use, depression and anxiety and poor QOL. Pain presentation was also not associated with the results of gastric emptying test, or with diabetic neuropathy or control of diabetes.

Early Satiety

In the same cohort, recent studies have evaluated the symptom of early satiety in 198 patients with gastroparesis (134 idiopathic, 64 diabetic) on the following treatments: 35% prokinetics; 80% on antiemetics and 35% narcotics. This study showed that

early satiety and postprandial fullness are commonly severe symptoms in both diabetic and idiopathic gastroparesis, and the severity of early satiety and fullness is associated with the severity of other gastroparesis symptom severities, body weight, quality of life (QOL), gastric emptying, and the volume of water that could be ingested in a water load test [11].

Epidemiology and Natural History

Given the high prevalence and socioeconomic impact of upper gastrointestinal symptoms in the United States [12], the prevalence of those symptoms are not higher in type 1 or 2 diabetes [13]. Epidemiological studies in Australia documented that postprandial fullness, and upper gut dysmotility symptoms of early satiety, postprandial fullness, bloating, nausea, or vomiting were more prevalent in 423 diabetics than in 8185 controls [14]; in a study of 1101 diabetics (209 outpatients and 892 diabetics in the community), dyspeptic symptoms were significantly associated with presence of neuropathy, poor glycemic control and female gender [15].

In Olmsted County, MN, the cumulative incidence of definite gastroparesis by combination of validated scintigraphic gastric emptying and symptoms was 4.8% in DM1, 1% in DM2, and 0.1% in controls. The crude incidence does not appear to be increasing between 1996-2000 and 2001-2006; however, diabetic gastroparesis persists despite improved glycemic control over 12 and 25 years [16,17], and there is evidence that gastroparesis is associated with increased mortality, visits to emergency department, and hospitalizations [18,19]. Diabetic gastroparesis may impair QOL across all SF-36 subscales independently of other factors, like age, tobacco, alcohol, type of DM [20,21].

Getting the Right Diagnosis for the Patient's Symptoms

There is increased recognition that the symptoms of gastroparesis may result not only from delayed gastric emptying, but also from several sensory or other motor disorders of the upper gut, including impaired gastric accommodation.

In a group of 1287 patients presenting to a tertiary care center with upper gastrointestinal symptoms, there was an approximately equal number with delayed gastric emptying, impaired gastric accommodation, a combination of both, or absence of both [22].This is consistent with the recognition that symptoms such as early satiety and postprandial fullness may result from impaired gastric accommodation, in addition to delayed gastric emptying. Getting the right diagnosis for the patient's symptoms is an essential first step (Figure 1).

Diagnostic Tests

Gastric emptying is best assessed with scintigraphy [23,24] or stable isotope breath test [25], which are well validated and for which normal control data are available. Impaired gastric accommodation is diagnosed with validated methods where available (SPECT [26] and MRI [27]), or with screening tests such as the size of the proximal

stomach on the gastric scintiscan taken immediately after radiolabeled meal ingestion [28], or by means of a water load [11] or nutrient drink test [29].

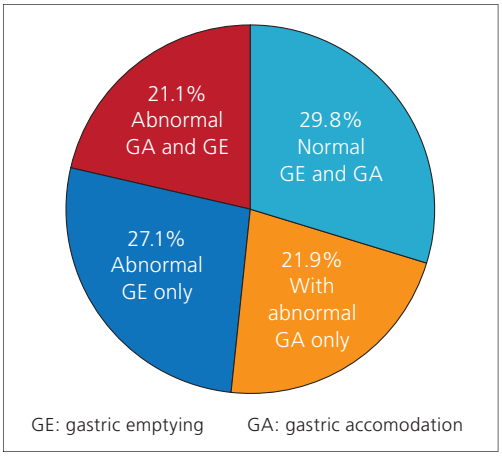

Figure 1: *Pie chart showing percentages of four groups of gastric motor functions in the 1,287 patients with upper functional gastrointestinal symptoms (from Park* et al. *[22])*

Differential Diagnosis

The main conditions to differentiate gastric neuromuscular dysfunctions are rumination syndrome [30,31], cannabinoid hyperemesis [32] and cyclic vomiting syndrome [33]. The common and uncommon causes of nausea and vomiting as well as the clinical features on history and examination, and pertinent blood and other investigations are discussed in detail elsewhere [34]. There is overlap betweek functional dyspepsia with delayed gastric emptying and gastroparesis.

Management

The management is discussed in detail in a recent publication [34], and this review will focus on a general treatment strategy that is based on the severity of the objective gastric retention at 4 hours, and the combination of diet, nutritional support, prokinetics, anti-emetics, symptom modulators, and non-pharmacological measures. These are summarized in Figure 2 [34], and the following text focuses on diet, new medical treatments relevant in gastroparesis and related disorders, treatments that are used off label to target the underlying mechanisms, and treatments targeting the pylorus.

a. Diet

A high-fat, solid meal increased overall symptoms among individuals with gastroparesis [35], and a small particle size diet reduced upper gastrointestinal symptoms (nausea, vomiting, bloating, postprandial fullness, regurgitation and heartburn) in patients with diabetic gastroparesis [36].

b. New Prokinetic Drugs for Gastroparesis

Relamorelin is a ghrelin receptor agonist that stimulates gastric body and antral contractions, accelerates gastric emptying, and has been shown in phase 2A and 2B studies to increase gastric emptying of solids and reduce symptoms, particularly nausea, fullness, bloating and pain [37,38]. Relamorelin is currently being tested in phase 3 trials, which should also provide information on optimal dose of this subcutaneous treatment.

Prucalopride (1-2mg/day), a 5-HT4 receptor agonist, is approved in most countries (other than USA) for the treatment of chronic constipation. It accelerates gastric emptying and was shown in a preliminary report to relieve symptoms in 28 patients with idiopathic gastroparesis [39].

c. New Drugs for Impaired Gastric Accommodation

Acotiamide has fundus-relaxing and gastro-prokinetic properties based on antagonism of the inhibitory muscarinic type 1 and type 2 autoreceptors on cholinergic nerve endings. It also inhibits acetylcholinesterase, enhancing gastric accommodation and emptying [40], and it relieves dyspeptic symptoms [41]. It is approved in Japan for treatment of dyspepsia.

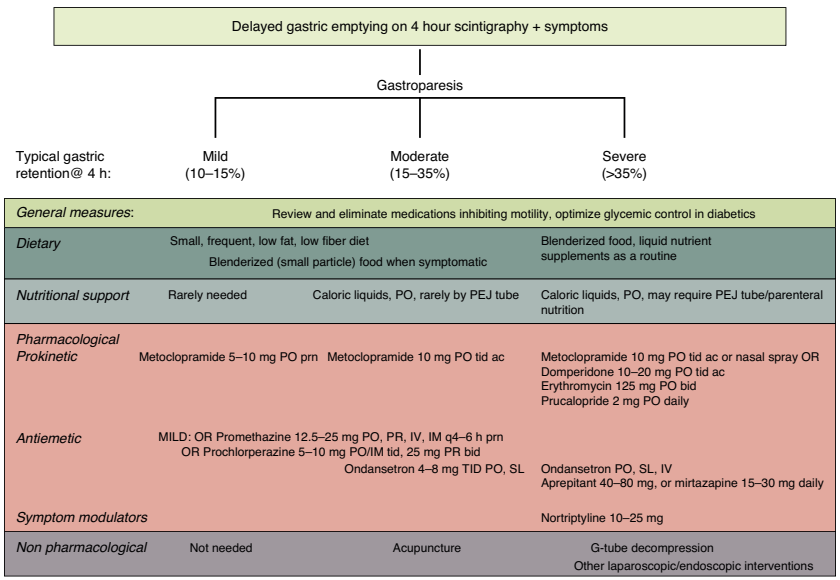

Figure 2: *Summary of treatment strategy for patients with gastroparesis (from Lacy* et al. *[34])*

d. Approved Drugs Used Off-label

Although not proven efficacious in a randomized, controlled trial in patients with gastroparesis [42], nortriptyline (tricyclic antidepressant) is used for relief of pain. In a study conducted in patients with functional dyspepsia, **amitriptyline** improved symptoms in patients who did not have delayed gastric emptying [43], and it modestly improved sleep quality [44]. The typical doses for both drugs are 25mg/day.

Mirtazapine (15mg/day), with its central adrenergic and serotonergic activity, provides symptom relief for patients with functional dyspepsia and weight loss, a condition with significant overlap with gastroparesis. Open label study with mirtazapine 15 mg PO qhs in patients with gastroparesis was associated with improvements in nausea, vomiting, retching and loss of appetite [45].

Buspirone (7.5-15mg daily or bid), a 5-HT1A agonist, enhances gastric accommodation and reduces postprandial symptoms in patients with functional dyspepsia [46].

Aprepitant (125mg/day) was efficacious in the treatment of nausea in some patients with gastroparesis and related disorders [47]. It does not change gastric emptying, but increases fasting and postprandial (accommodation) gastric volumes [48].

e. Pyloric Interventions

Open-label experience with intra-pyloric BOTOX injection in 179 patients with gastroparesis was associated with decrease in gastroparesis symptoms 1 to 4 months after pyloric BOTOX in 92 patients (51.4%). Improved response to BOTOX was observed in those who received 200U (rather than 100U), females, age <50 years, and non-diabetic, non-postsurgical gastroparesis patients [49].

Pyloroplasty performed surgically or endoscopically is being offered to patients who are refractory to other treatments, including pharmacological approaches, enteral feeding and gastric electrical stimulation. The basic rationale for this approach is the observation of pylorospasm in patients with gastroparesis, particularly diabetic gastroparesis [50]. It is unclear whether factors such as the presence of concomitant antral hypomotility, or differences in pyloric compliance (for example as a result of scarring) impact the efficacy of pyloric interventions.

An analysis of 7 studies [51] included 130 patients with a mean follow-up ranging from 3-12 months, and the main etiologies were idiopathic (44.5%), diabetic (30.8%), and post-vagotomy (20.5%). Overall, pooled proportions of clinical success were 87.01 (CI: 76.6-94.6) %, (Figure 3A), and gastric emptying was normalized in 62.6 (CI 49.9-74.5) % of cases (Figure 3B); adverse events were observed in 7.6 (CI: 1.96-16.5) % of cases.

Controlled studies are required to assess efficacy of pyloric interventions. Meanwhile, we have proposed the algorithm in Figure 4 [34] that may be used to guide selection of patients for pyloric interventions.

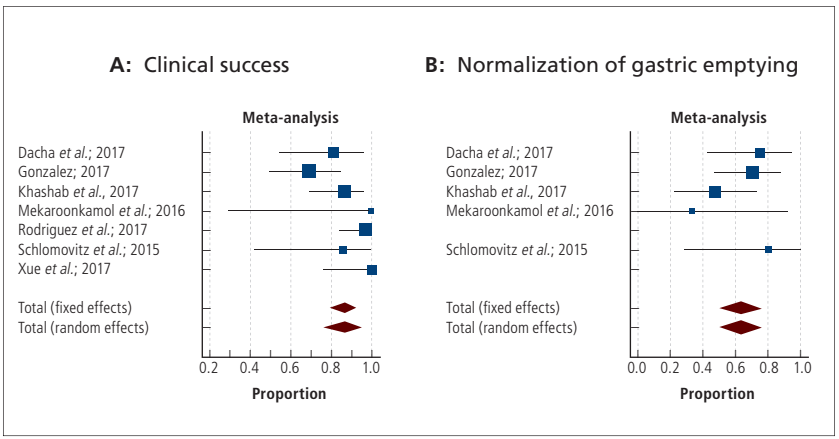

Figure 3: *G-POEM improves clinical symptoms and gastric emptying in gastroparesis: a systematic review and meta-analysis (from Avalos* et al. *[51])*

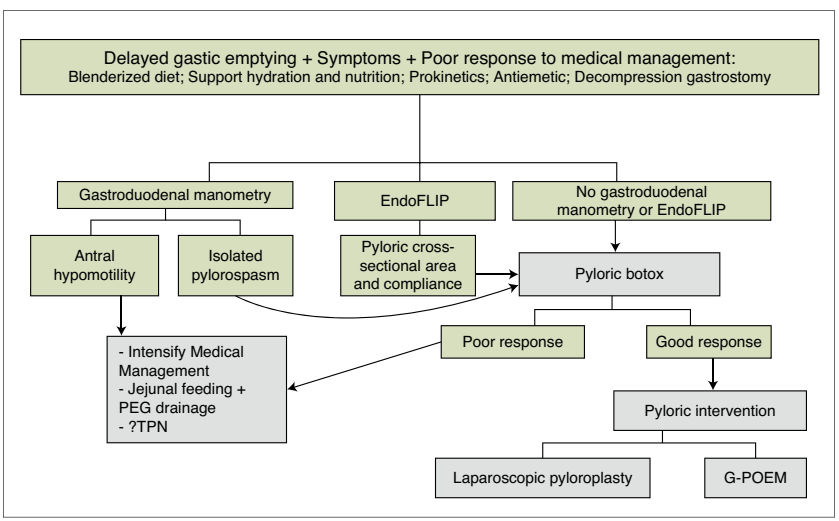

Figure 4: *Proposed algorithm for pyloric interventions for gastroparesis unresponsive to medical treatment (from Lacy* et al. *[34])*

Gastric Electrical Stimulation for Gastroparesis

While there are a number of open label studies suggesting effeicacy of gastric electrical stimulation (GES) in treatment of gastroparesis, particularly diabetic gastroparesis, the two systematic reviews and meta-analyses recommend caution in adopting GES outside research studies, citing regression to the mean in the assessment of symptoms and insufficient efficacy based on the few controlled trials comparing off *versus* on GES treatment [52,53].

Conclusions

Important advances in gastroparesis and related disorders include treating patients with symptoms suggestive of gastroparesis based on the right diagnosis, excluding iatrogenic disease and use of opioids. New pharmacologic agents are promising; meanwhile off-label use of approved medications anchors current management in addition to dietary interventions. Pyloric interventions, including endoscopic pyloroplasty, require further validation.

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Massimo Rugge

12:00 The Way Forward Gastric Cancer:
Helicobacter pylori Infection and Gastritis

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Introduction
Before the year is out, more than one million new cases of gastric cancer (GC) will have been diagnosed worldwide. Due to the advanced stage of the cancer at the time of its clinical assessment, the overall 5-year survival rate of these patients will not exceed 30% [1-3].

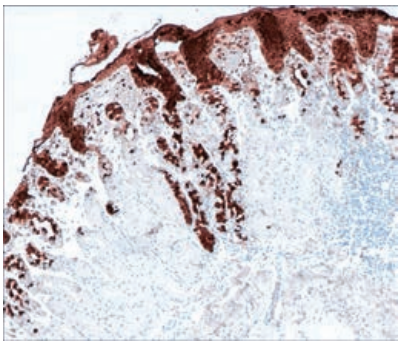
GC is an epithelial malignancy, usually arising through a stepwise accumulation of genotypic and phenotypic changes triggered by a longstanding gastritis, mostly due to *Helicobacter pylori* (*H. pylori*).

The assessment of gastritis-associated GC risk depends on several etiologic factors, which are both environmental and host-related. Once the (rare) cases of syndromic GC have been excluded [4], the gastric mucosal atrophy is the greatest risk factor for non-hereditary GC. Consistent evidence correlates the extent/topography of mucosal atrophy with the cancer risk. This means that either noninvasive (serology) or invasive (endoscopy/histology) methods enabling the atrophic transformation to be detected/quantified can theoretically be applied in the assessment of GC risk [5,6].

Atrophic Gastritis: the Natural History
Worldwide, *H. pylori* infection is the most prevalent etiology of gastric mucosa atrophy. Because of the earliest antral location of *H. pylori*-associated inflammatory lesions, the distal gastric mucosa (including its cranial "atrophic" border) is the gastric compartment exposed the soonest to the risk of atrophy [7]. The progressive distal-to-cranial spread of the inflammatory lesions later involves the oxyntic mucosa, eventually resulting in pan-gastric (patchy) atrophy (so called Correa's *multifocal atrophic gastritis*). This atrophic phenotype is the elective background in which neoplastic lesions may develop [8].

Less commonly, gastric atrophy may result from a primary autoimmune disease, targeting the (oxyntic) parietal cells which change their native acid-secreting commitment and

acquire the metaplastic morphology of pyloric glands (i.e. pseudo-pyloric metaplasia, also known as spasmolytic polypeptide-expressing metaplasia [SPEM] (Figure 1) [9-11].



SPEM after **Tff2**-immunostain

SPEM on H&E \ SCORE	0	1	2	3	T
0	0	0	0	0	0
1	0	8	2	0	10
2	0	0	11	14	25
3	0	0	0	15	15
T	0	8	13	29	50

Cohen's ***k*** test= 0,46 (.0001); CI=15%-75%

50 oxyntic mucosa biopsy samples of 50 Autoimmune Gastritis patients. In all cases, SPEM has been scored on both H&E and Tff2 immunostain (unpublised).

Figure 1: *Pseudo pyloric (metaplastic) glands have to be distinguished from the native pyloric (mucosecreting) glands. TFF2 immunostain consistently identifies (brown color) the metaplastic glands. The table demonstrate how the TFF2-immunostain increases the sensitivity of the routine Hematoxylin-Eosin in the identification of the SPEM-glands (p<.0001)*

Notably, *H. pylori* infection has been reported to potentially trigger a "secondary autoimmune" inflammation targeting the parietal cells of the oxyntic mucosa [12,13]. It is still unclear, however, whether this *H. pylori*-induced autoimmunity is due to a host's specific immunological attitude, or to a peculiar *H. pylori* biological profile, or even both.

Atrophy: Definition and Histological Phenotypes

Gastric atrophy is defined as loss of *appropriate glands* [14]. This definition includes two phenotypes of atrophic transformation (Table 1):

i) disappearance of glandular units, replaced by fibrotic lamina propria (*i.e. non-metaplastic atrophy*); or
ii) replacement of the native by metaplastic glands featuring a new commitment (*i.e. metaplastic atrophy*) involving intestinal metaplasia (IM), and/or pseudo-pyloric metaplasia (SPEM) [15-20] (Figure 2).

In each biopsy sample, atrophy can be scored as percentage of the atrophic transformation. Including a score of 0 (i.e. no atrophy), a 4-tiered scale has been proposed, where a score of 1 = global (i.e.: non-metaplastic and metaplastic atrophy) atrophy affecting 1-30% of the biopsy sample; 2 = global atrophy affecting 31-60% of the biopsy sample; and 3 = global atrophy affecting more than 60% of the biopsy sample. Such a scoring, which includes all the (frequently coexisting) histological variants of atrophy, can be consistently applied to any biopsy sample as obtained from either the antral (including the *incisura angularis*), or the oxyntic mucosa.

Table 1: Nosology, histology phenotypes, and score method for gastric mucosa atrophy

Atrophy	Histological Type	Site/Type of Lesions		Histology Score
		Antral mucosa including the incisura angularis	Oxyntic mucosa	
Absent				Score 0
Indefinite		High-grade inflammation	High-grade inflammation	Not assessable
Present	NON-METAPLASTIC (decline in number of native glands)	Glands vanishing/shrinking Fibrosis/inflammation of the lamina propria	Glands vanishing/shrinking Fibrosis/inflammation of the lamina propria	Score 1= 1-30% Score 2= 31-60% Score 3= >60%
	METAPLASTIC (metaplasia of native glands)	Intestinal metaplasia	Pseudo-pyloric metaplasia (SPEM) Intestinal metaplasia	

Endoscopy Biopsy Sampling

Any gastrointestinal endoscopy procedure can never be considered "complete" unless a biopsy set is obtained. Several protocols of gastric biopsy sampling have been proposed [21,22]; among them, the most applied is that recommended by the Sydney System, which includes 2 biopsy samples from the oxyntic mucosa, 2 from the antral, and 1 form the *angularis incisura* (Figure 3) [23].

The tissue samples should be submitted to the Pathology department in (at least) two separate vials: one containing the antral and *angularis* samples, the other the oxyntic biopsies. The *angularis* incisura has been considered as "sentinel" site, where any atrophic transformation is assessable soonest. Sampling the *angularis* mucosa is time-consuming, however, and many endoscopists would prefer to skip this sampling-step. Additional samples should be obtained from any focal lesions, including ulcers (especially in the proximal stomach) and/or elevated/polypoid lesions.

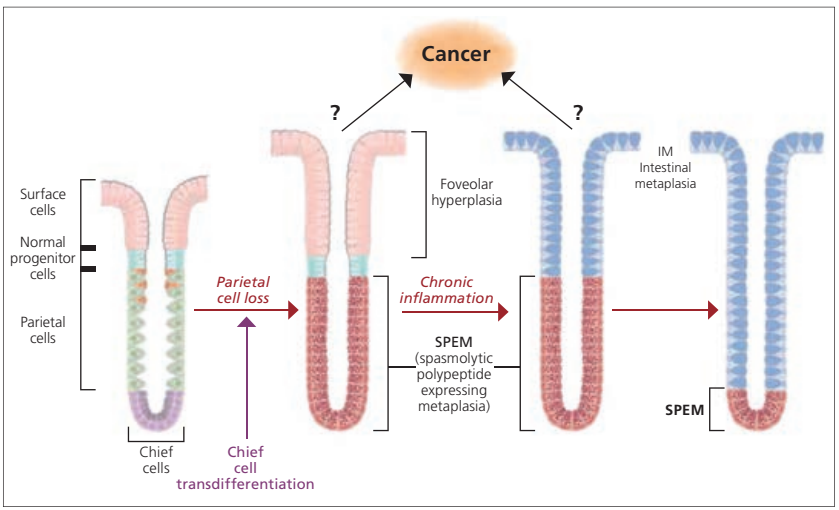


Figure 2: *A revised model for the evolution of metaplasia in the stomach. Loss of parietal cells leads to evolution of SPEM at the bases of glands from transdifferentiation of chief cells. With continuing chronic inflammation, intestinal metaplasia develops within the luminal aspect of SPEM glands. Over time, intestinal metaplasia comes to dominate over SPEM in metaplastic mucosa. In remains to be determined whether gastric cancer arises form SPEM or from proliferative intermediates generated during the further differentiation of SPEM into intestinal metaplasia (from Goldenring* et al. *[15])*

Histology Reporting: from a Descriptive to the Staging Approach

The current knowledge of gastritis natural history, and the criteria applied in the histological assessment of atrophy both represent the groundwork beyond reporting gastritis in terms of stage and grade. This approach replaces the descriptive "Sydney model" [23]. *Grading* refers to the "overall grade" of the inflammation, while *Staging* conveys information on the severity/location of the atrophic-metaplastic changes. The "grading/staging proposal", formally suggested by an international group of experts (the Operative Link for Gastritis Assessment [OLGA system]) [24,25], includes two "compartmental" scores for atrophy, one based on the antral/*angularis* biopsy samples, the other on the oxyntic samples (each scored as: 0, 1, 2, 3). By combining the antral with oxyntic atrophy-scores, the OLGA gastritis staging distinguishes 5 stages (0 to IV), theoretically associated with different GC risk (Table 2). Several studies, conducted in different epidemiological settings, associated only with stages III and IV an increased risk of GC development. Otherwise speaking, the OLGA stage is able to identify the

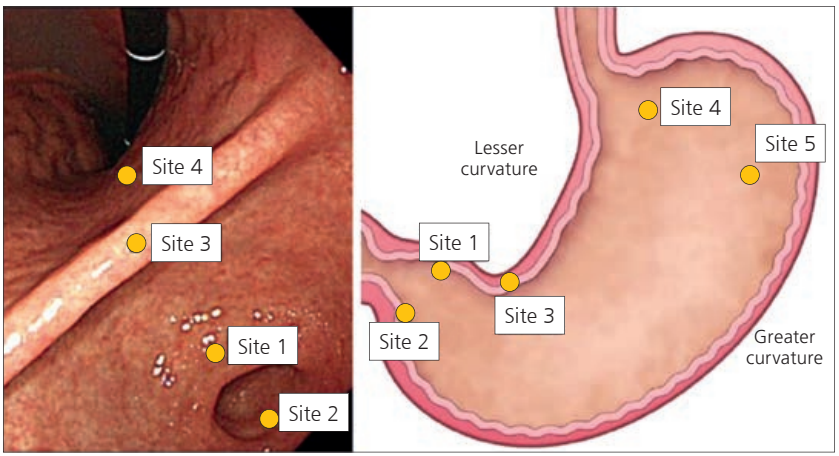


Figure 3: *Location of biopsy sites according to the updated Sydney system*

individual likelihood of a patient to develop a malignancy, and can be adopted to tailor the endoscopic follow-up based to the individual-patient GC risk. Because IM histological scoring was judged more consistent than atrophy scoring, an alternative staging system (OLGIM) was subsequently proposed, which is based only on the IM score [26].

Further investigations are needed to compare these two staging proposals; but both are basically consistent with the aim to unequivocally identify those gastritis patients who should be placed under surveillance.

"Gastric Serology" in GC – Secondary Prevention Strategies

Both the invasiveness and cost of endoscopy and biopsy procedures limit their extensive use as first-line approach for GC secondary prevention. Serological tests have therefore been proposed as non-invasive (first-line) method for identifying those atrophic gastritis patients who might warrant endoscopic (second-line) investigation. The serological assessment of gastric atrophy is largely based on two main pro-enzymes produced by the gastric mucosa: Pepsinogen I (PGI), Pepsinogen II (PGII), and their ratio (PGI/PGII). While PGII is produced by both the antral (mucosecreting) and corpus (specialized) mucosa, PGI is produced almost exclusively by the oxyntic cells (Figure 4). This implies that any atrophic loss of the oxyntic glands closely reflects in less PGI serum levels and, consequently, in decreasing the PGI/PGII ratio [27].

Table 2: OLGA staging frame

Atrophy (any subtype) at single biopsy level: • Score 1= 1-30% • Score 2= 31-60% • Score 3= >60%	Mean percentage of atrophy as assessed in 2 specimens obtained from the OXYNTIC MUCOSA				
		Score 0	Score 1	Score 2	Score 3
Mean percentage of atrophy as assessed in 3 specimens obtained from the ANTRAL MUCOSA (including incisura angularis)	Score 0	0	I	II	II
	Score 1	I	II	II	III
	Score 2	II	II	III	IV
	Score 3	III	III	IV	IV

In case of *H. pylori* gastritis, a normal PGI/PGII ratio virtually rules out the presence of any gastric mucosal atrophy (with a high-negative predictive value) and, therefore, the patient may be confidently excluded from any further endoscopic procedure. Among *H. pylori* infected subjects, a low PGI/PGII ratio prompts to consider a second-line endoscopy/histology exanination (Figure 5). The cut-off to distinguish patients at risk on serology may differ, depending on the population-related cancer risk.

Gastritis Staging in International Guidelines

In 2002, an expert consensus statement suggested that *H. pylori* eradication therapy can prevent gastric cancer [28]. In 2009, the Asia-Pacific consensus guidelines recommended an eradication strategy in countries with a high incidence of GC [29].

In 2012, an international consensus document on the Management of precancerous conditions and lesions in the stomach (MAPS) stated that:

"Systems for histopathological staging … may be useful for identifying subgroups of patients with different risks of progression to gastric cancer (recommendation grade C), namely those with extensive lesions (i.e., atrophy and/or intestinal metaplasia in both antrum and corpus)" [30]. Gastritis staging, however, was not mentioned among the crucial variables to distinguish atrophic gastritis by different levels of GC risk.

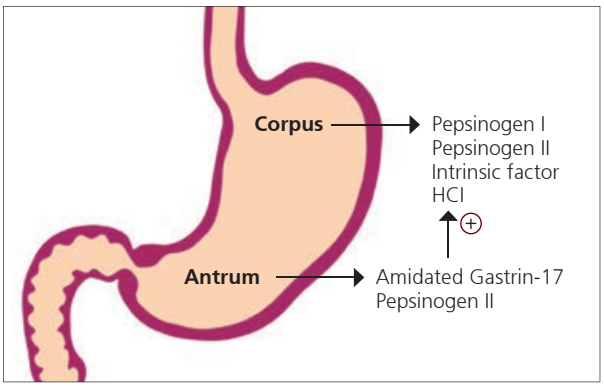


Figure 4: *Pepsinogens and gastrin G-17 production from the gastric corpus and antrum*

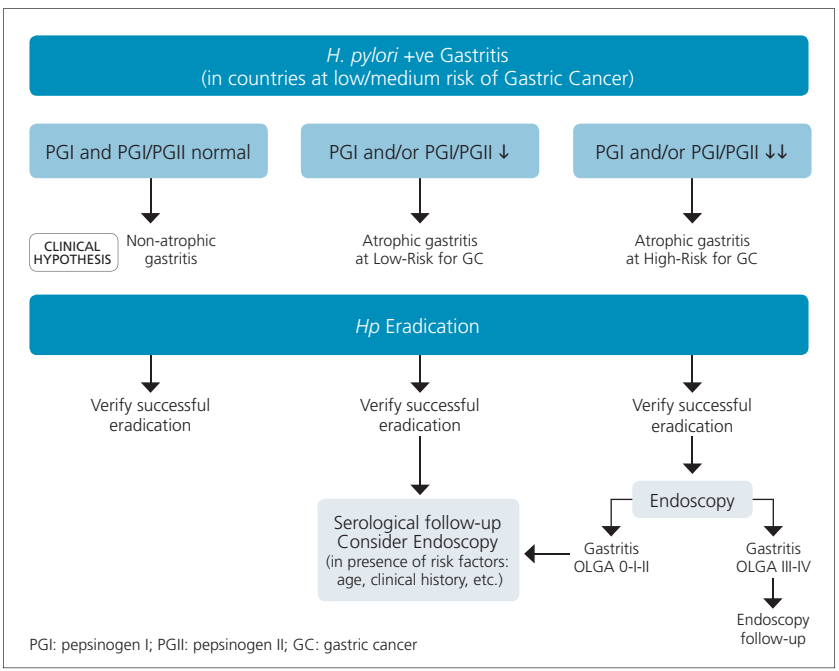


Figure 5: *Gastric serology and clinical management at H. pylori (Hp) positive gastritis*

In the same year, the Maastricht IV/Florence Consensus Report recommended the use of gastritis staging in the routine management of gastritis patients and reported:

"The gastritis OLGA staging conveys useful information on the potential clinico-pathological outcome (including cancer progression). The adoption of this system is therefore useful for patient management. According to OLGA staging and H. pylori status, patients with gastritis can be confidently stratified and managed according to their cancer risk" [31].

In February 2014, the Kyoto Global Consensus Conference unanimously recognized that the risk of GC reflects the atrophy extent/topography, as assessed by gastritis staging. More precisely, according to Statement No. 4 (consensus level: 100%):

"New staging systems for the characterization of gastritis have been introduced to assess the gastric cancer risk. They are used in clinical practice and are either based on the severity of atrophy in various gastric sub-sites (OLGA) or on intestinal metaplasia (OLGIM)" [32]. The same document (Statement No.14) qualifies the histological staging of gastritis as: *"useful for risk stratification (Grade of recommendation: strong; Evidence level: low; Consensus level: 97.3%)".*

More recently, in 2015, both the Maastricht V/Florence Consensus Report [33] and the "Guidelines for the management of *Helicobacter pylori* infection in Italy" [34] have included gastritis staging among the clinico-pathological procedures to be applied to the strategies of gastric cancer secondary prevention.

Conclusions

More than 40 years ago, by describing its "gastric oncogenetic cascade", Pelayo Correa provided the biological rationale for GC prevention. The subsequently-emerging evidence of *H. pylori* being responsible for triggering the GC-promoting inflammation made theoretically possible the primary cancer prevention.

As for secondary GC prevention, it is basically founded on the clinico-pathological assessment of GC precursor lesions: atrophic gastritis, and gastric epithelial dysplasia. This strategy basically demands a task-force including a trio of specialists (endoscopist, gastroenterologist, pathologist). Currently, by applying the available digital images, endoscopists can capture minute mucosal lesions that were invisible 15 years ago; pathologists are asked to deliver diagnostic messages (i.e., to stage cases of gastritis) that can be used consistently to rank a given patient's cancer risk; gastroenterologists, finally, are in charge of providing appropriate anti-*H. pylori* therapies (where necessary) and establishing patient-tailored follow-up protocols [35,36].

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CURRENT AND FUTURE
MANAGEMENT OF DIGESTIVE
DISEASE: FROM BENCH TO BEDSIDE

Notes


Guido Costamagna

12:30 UGIB: Management in the Era of Novel Antithrombotic Therapies

Guido Costamagna, MD, FACG

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Vitamin K antagonists (VKAs, represented mainly by warfarin) are widely and effectively used in the prevention of thromboembolic events since decades. However, VKAs are associated with major limitations: they have a narrow therapeutic window, variable and unpredictable pharmacokinetics and pharmacodynamics, many drug-to-drug and food-to-drug interactions, slow onset and offset of action. All these drawbacks oblige to a constant and regular monitoring and dose adjustments, which are cumbersome for the patients and expensive for health care systems [1,2].

Novel oral anticoagulants (NOACs) have been recently introduced into clinical practice and include direct thrombin inhibitor (***dabigatran*** – Pradaxa® Boehringer-Ingelheim Pharma GmbH Germany) and direct factor Xa inhibitors (***rivaroxaban*** – Xarelto® Johnson&Johnson/Bayer Healthcare Germany, ***apixaban*** – Eliquis® Bristol Myers Squibb/Pfizer UK, ***edoxaban*** – Lixiana® Daiichi Sankyo Japan) (Figure 1) [3]. NOACs are increasingly employed instead of warfarin, and are currently used mainly in the prevention of thromboembolic events in patients with atrial fibrillation or deep vein thrombosis. Compared to warfarin, NOACs have much more predictable pharmacokinetics and pharmacodynamics, fewer food and drug interactions and a much prompt onset and offset of action [4].

Despite a good safety profile shown by several meta-analyses and phase IV studies, NOACs may induce haemorrhagic events in high-risk patients, especially in the gastrointestinal (GI) tract. This short review will deal with the risk factors for GI bleeding related to commonly prescribed NOACs, their prevention and treatment approaches.

Dabigatran is a direct and reversible inhibitor of thrombin activity. It is administered as a pro-drug (dabigatran etexilate), which is converted into the active drug by serum and hepatic esterases after absorption in the proximal small bowel [5]. The bioavailability of dabigatran etexilate is very small (only 7%), the majority of unabsorbed

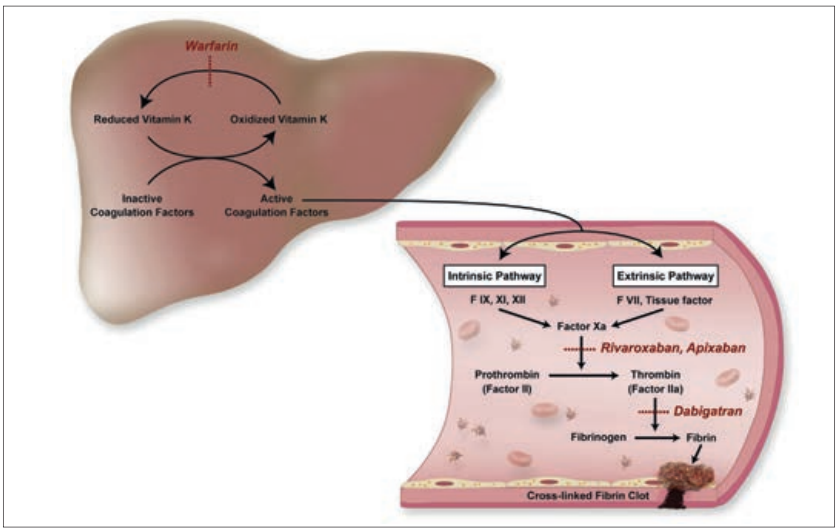

Figure 1: *Sites of action of warfarin, apixaban, dabigatran, and rivaroxaban. Warfarin inhibits the synthesis of the vitamin K-dependent clotting factors (II, VII, IX, and X) in the liver, whereas the novel oral anticoagulants competitively inhibit the binding of factor Xa (apixaban and rivaroxaban) or thrombin (dabigatran) to their substrates in the blood. F, factor (from Desai* et al. *[3])*

drug remaining into the GI lumen and being finally excreted in the stools. On the contrary, the bioavailability of the inhibitors of factor Xa is much higher compared to dabigatran (rivaroxaban 66%, apixaban 50%, edoxaban 60%) [6,7]. Severe renal impairment and advanced liver disease are the main contraindications of NOACs.

The mechanisms by which NOACs may induce GI bleeding are multiple [3]. These are both systemic and local. Of note, the local effect is produced by a combination of a local anticoagulant effect, the inhibition of mucosal healing, and, in the case of dabigatran, a direct caustic injury caused by tartaric acid contained in the unabsorbed prodrug (Figura 2)[8]. Compared to warfarin, dabigatran and rivaroxaban are associated with an increased risk of bleeding only at the GI level, but not in other organs (Figura 3) [4,8]. Interestingly enough, also the sites of GI bleeding are different for NOACs. While the upper GI tract is the predominant source of drug-induced bleeding from low-dose aspirin, non-steroidal anti-inflammatory drugs or warfarin, lower GI bleeding may account for more than 50% of the cases in dabigatran users [9]. This is probably due to the topical effect on the mucosa, exerted by the incompletely absorbed drug, which may lead to bleeding, especially in the presence of predisposing

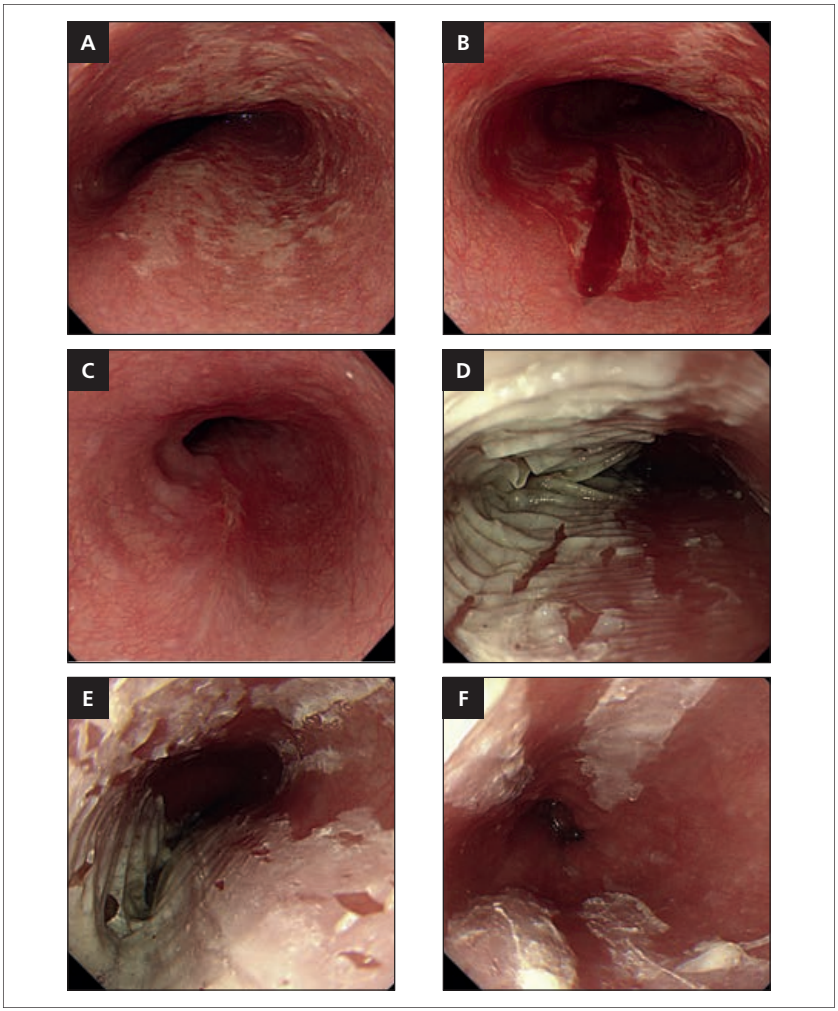

Figure 2: *Dabigatran-induced esophagitis;* A) *"kissing erosions" at the anterior and posterior wall of the broncho-aortic constriction in the midesophagus;* B) *linear tear;* C) *follow-up with disappearance of erosions and a linear ulcer scar;* D-F) *longitudinal sloughing mucosal casts in the middle to distal esophagus, with sparing of the squamocolumnar junction (from Ootani* et al. *[7])*

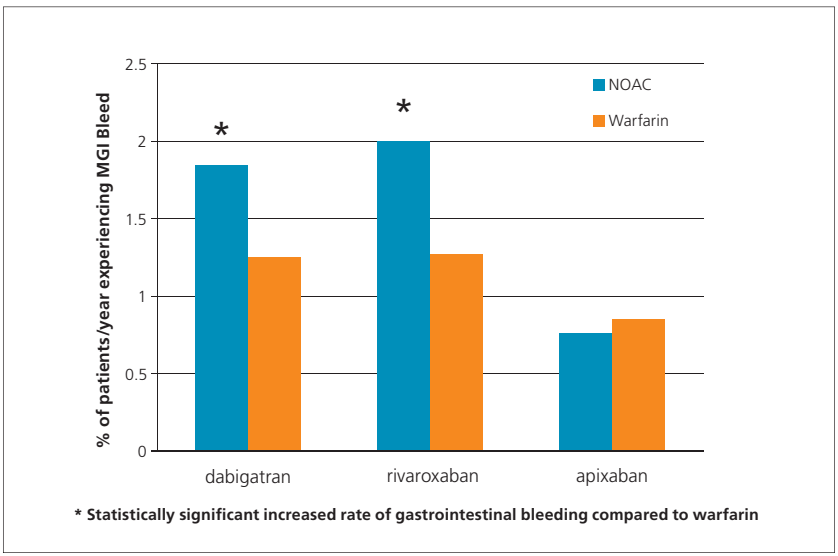

Figure 3: *The rate of major gastrointestinal bleeding in the 3 pivotal novel oral anticoagulant trials (NOAC compared with warfarin). Note that in the ROCKET-AF (rivaroxaban) and ARISTOTLE (apixaban) trials, definition of major bleeding required bleeding to be clinically overt, whereas in the RE-LY (dabigatran) trial, this was not required (from Desai* et al. *[3])*

lesions such as erosions or angiodysplasias [5]. On the contrary, rivaroxaban produces more upper than lower GI bleeding (76% *versus* 24%) [10], while the risk for upper and lower bleeding is approximately the same in high-dose edoxaban users.

The risk of GI bleeding in patients undergoing treatment with NOACs has been recently evaluated in a meta-analysis (Figure 4) [11], including 17 RCTs and a total of 75.081 individuals, receiving either NOACs or standard care (VKAs, low molecular weight heparins, antiplatelet agents or placebo): there was a 1.5% incidence of GI bleeding over 3 years follow-up, 89% being major bleedings. Compared with standard care, there was an increased risk of GI bleeding in NOACs users (OR 1.45). This was true both for dabigatran (OR 1.58) and rivaroxaban (OR 1.48), but not for apixaban and edoxaban. The highest risk was seen in patients with acute coronary syndrome, in whom NOACs were associated to antiplatelet drugs (OR 5.21). Furthermore, in patients treated with dabigatran, a higher risk of GI bleeding was only detected when the higher dose (i.e. 150 mg b.i.d.) was used, suggesting a dose-related effect [11].

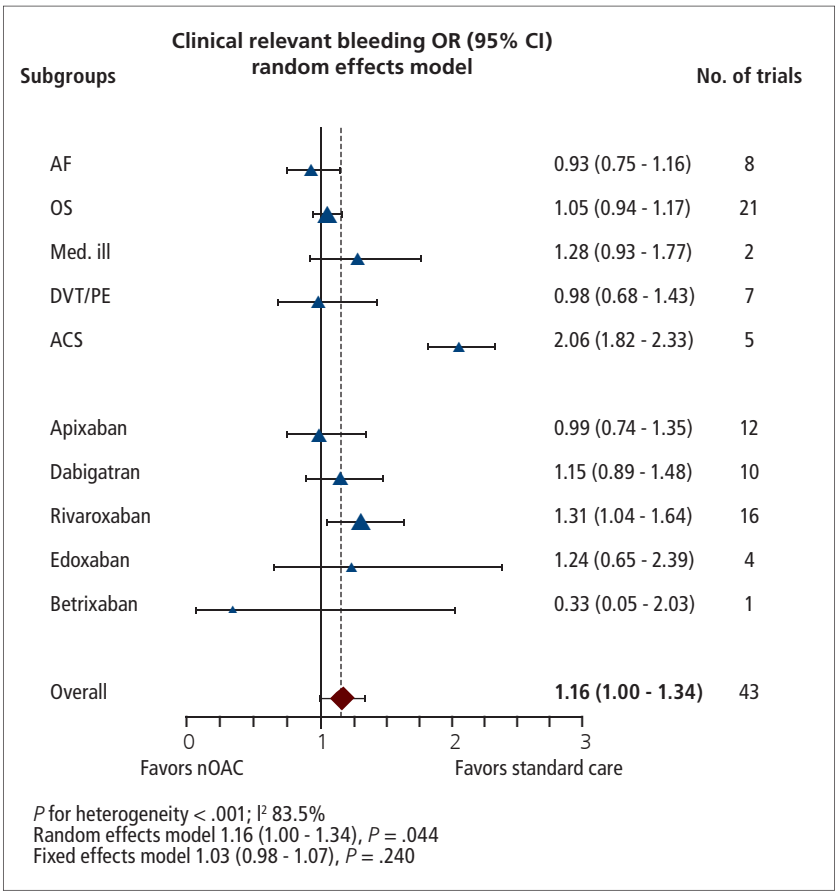

Figure 4: *Forrest plot of clinically relevant bleeding summarized by indication and by drug. Data are presented as OR (95% CI) using a random effects model and an I^2 test for heterogeneity (ACS: acute coronary syndrome; AF: atrial fibrillation; DVT: deep vein thrombosis; Med ill: medically ill; OS: orthopedic surgery; PE: pulmonary embolism) (from Holster* et al. *[11])*

To evaluate the risk of GI bleeding related to NOACs use in real life settings, a recent meta-analysis, including 8 cohort studies and 117.339 individuals, was recently published [12]. Compared to warfarin, dabigatran was associated with an increased risk

of GI bleeding (RR 1.21), but not rivaroxaban. However, quite the reverse, in another observational comparative study on 118.891 patients aged 65 years or more undergoing anticoagulation for atrial fibrillation [13], rivaroxaban was associated with a higher risk of major GI bleeding compared to dabigatran (HR 1.40). Confounding factors, almost always present in observational studies, are the major concern in interpreting the results of meta-analyses.

There are several risk factors associated with the NOAC-related gastrointestinal bleeding [14]:

- Higher doses of dabigatran (150 mg b.i.d.) and of edoxaban (60 mg daily)
- Concomitant use of ulcerogenic agents (nsaids, steroids, antiplatelet agents)
- Older age (> 75 Years)
- Renal impairment (creatinine clearance <50 ml/min)
- Prior history of peptic ulcer or GI bleeding
- *Helicobacter pylori* infection
- Pre-existing gastrointestinal lesions (i.e. diverticulosis, angiodysplasias, etc.)
- Ethnicity (western population)
- HAS-BLED score (multifactorial bleeding risk score) >3 [15]

The simultaneous use of proton pump inhibitors (PPIs) or histamine H_2-receptor antagonists (H_2RAs) is considered a protective factor, with a 50% reduction in the risk of GI bleeding [16]. However, this protective effect seems to be limited to the upper GI tract and in those patients with a history of peptic ulcer disease and/or prior bleeding.

The mainstay of bleeding prevention relies on ***identification of contraindications*** of NOACs administration (mainly renal function impairment and advanced liver disease with coagulopathy) [17], and on ***the treatment of modifiable risk factors*** (i.e. eradication of *Helicobacter pylori* infection, alcohol abstinence, avoidance of co-administration of NSAIDs and antiplatelet agents, etc). In patients with high bleeding risk identified by an HAS-BLED score >3 and/or by previous episodes of gastrointestinal bleeding, prescription of PPIs or H_2RAs is recommended, alongside with low-dose dabigatran (110 mg b.i.d.) or apixaban [4,8].

Of note, treatment with NOACs may lead to an earlier detection of GI tract neoplastic lesions as they may facilitate bleeding of these lesions [18]. Screening colonoscopy has therefore been suggested to detect occult tumours before initiation of NOACs, in order to reduce the risk of tumour-associated bleeding. However, this policy is not currently recommended by the guidelines of most scientific societies.

Treatment of patients that present with overt minor GI bleeding includes interruption of the NOACs administration and endoscopic management like the one adopted for non-anticoagulated patients [4,8]. In patients with normal renal function, discontin-

uation of the drug will allow a prompt return to a normal coagulation pattern within 12-24 hours. If severe bleeding occurs, with or without hemodynamic instability, other measures may be taken into consideration. Activated charcoal administration, in order to reduce the intestinal absorption of the residual drug into the GI tract may be considered, if the last dose has been assumed less than 2 hours before. However, the potential benefit of charcoal administration may be counterbalanced by the impaired endoscopic visualization leading to a less effective endoluminal treatment, when needed. Only in the case of life-threatening bleeding or renal failure, and only for dabigatran, hemodialysis or hemoperfusion may be envisaged.

The use of non-specific reversal agents (i.e. prothrombin complex concentrates, recombinant factor VIIa) and of anti-fibrinolytic agents (tranexamic acid) is not well studied and of uncertain efficacy. Again, these measures should be employed only in case of life-threatening bleeding, impaired renal function and persisting bleeding despite standard care [17].

Specific reversal agents (antidotes) have been recently introduced into clinical practice. *Idarucizumab* is a humanized antibody fragment (Fab) specific to dabigatran: its binding affinity for dabigatran is approximately 350 times higher than dabigatran to thrombin, resulting in essentially irreversible binding. Idarucizumab is ready to use in vials for i.v. administration (5g, 2 x 2.5 g i.v.), has an immediate onset of action, and no intrinsic procoagulant or anticoagulant activity. The Fab-drug complex is eliminated quickly, within a few hours. Idarucizumab is able to fully reverse anticoagulation in approximately 90% of the patients [19]. *Andexanet* alfa is a recombinant modified human factor Xa, specifically designed to reverse anticoagulant effects of factor Xa inhibitors, and acts as a factor Xa decoy to bind molecules that target and inhibit factor Xa. Andexanet alfa has been shown to achieve hemostasis in up to 80% of patients with acute major bleeding [20]. Unfortunately, the thromboembolic risk associated with the administration of these antidotes is not negligible, being 5% for idarucizumab and 18% for andexanet alfa [19,20].

Data concerning the endoscopic management of gastrointestinal bleeding in patients undergoing treatment with NOACs are scanty. However, according to expert opinions, the endoscopic approach, in this setting, does not substantially differ from the one applied to the general population (Figure 5) [21]. The timing of endoscopy depends on the severity of the bleeding and hemodynamic status of the patient. As in the general population, endoscopy can be postponed at 12-24 hours in patients with mild bleeding, when the effects of NOACs will be attenuated [3,22]. There are several theoretical advantages of this approach: increased efficacy of endoscopic intervention in a patient, who has recovered a normal coagulation status, increased safety in a non-emergency setting, improved endoscopic visualization related to diminution or cessation of bleeding, increased time to achieve colon cleansing, when indicated.

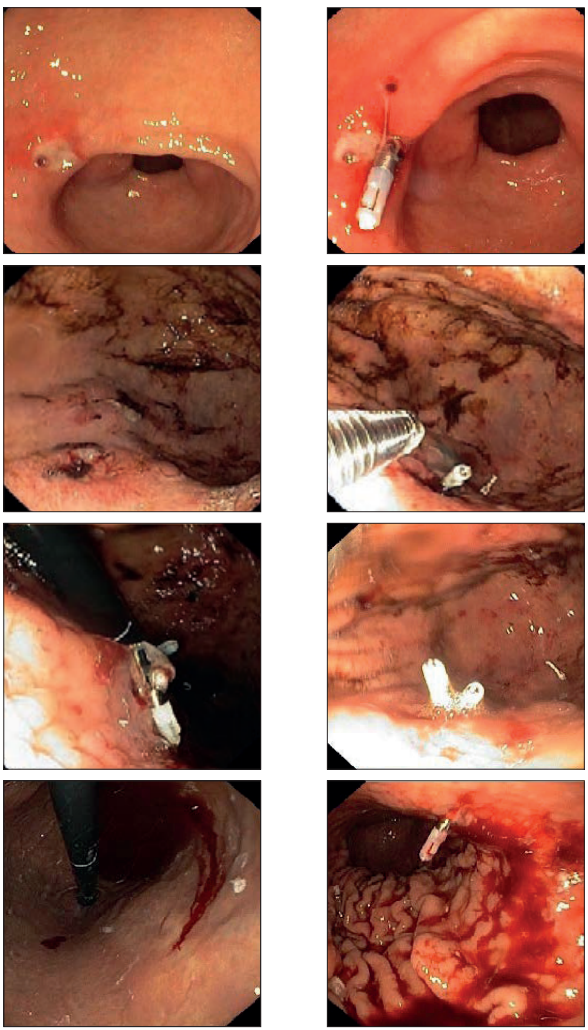

Figure 5: *Endoscopic lesions found in patients who were anticoagulated at the time of the endoscopy (note the frequently used endoscopic hemoclips) (from Oprita* et al. *[21])*

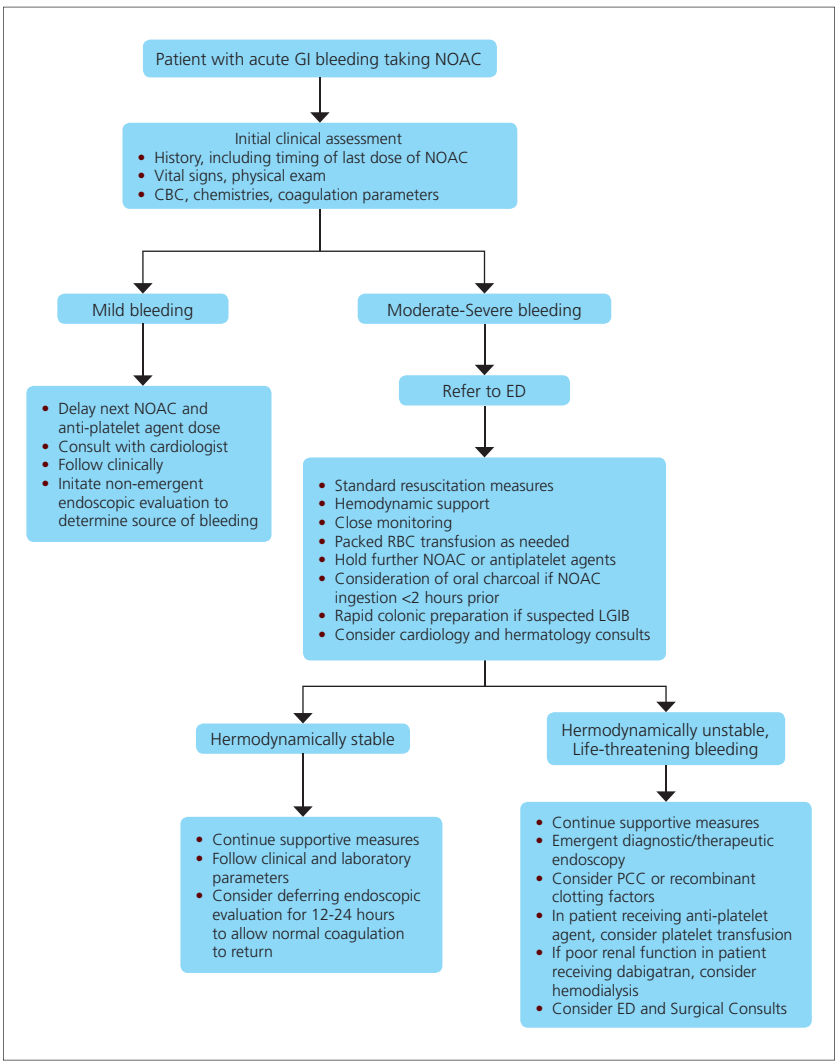

Figure 6: *Suggested algorithm for GI bleeding management in the patient receiving novel oral anticoagulant therapy (from Desai* et al. *[8])*

Because of the relative propensity of NOACs to provoke lower GI bleeding, rapid colon cleansing followed by colonoscopy may be often useful [3].

If patient presents with severe GI bleeding or is hemodynamically unstable, endoscopy should be performed early after resuscitation and stabilization of the hemodynamic profile, as in the general population. Radiological and/or surgical interventions should be considered only in case of repeated failure of the endoscopic approach in obtaining hemostasis. An algorithm of the endoscopic management of patients with GI bleeding taking NOACs is reported in Figure 6.

In conclusion, GI bleeding may be a severe complication of anticoagulant treatment, and, in some instances, it may favour early detection of cancer, particularly in subjects treated with NOACs. Presence of anticoagulant activity in the GI lumen is likely to be the main reason for the relatively high incidence of GI bleeding with NOACs. Antidotes, when available, are a very effective tool for bleeding management in patients undergoing NOACs therapy.

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MANAGEMENT OF DIGESTIVE
DISEASE: FROM BENCH TO BEDSIDE

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FRIDAY, November 9, 2018 – Afternoon

SESSION II:
SMALL AND LANGE BOWEL

CHAIRED BY:


Jimmy K. Limdi

Jimmy K. Limdi, MBBS, FRCP (Lond & Ed), FEBGH, FACN, FACG
Consultant Physician & Gastroenterologist Pennine Acute Hospitals NHS Trust and Institute of Inflammation and Repair, Manchester Academic Health Sciences Centre, 46 Grafton Street, Manchester, UK

Governor for UK, American College of Gastroenterology


CURRENT AND FUTURE
MANAGEMENT OF DIGESTIVE
DISEASE: FROM BENCH TO BEDSIDE

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FRIDAY, November 9, 2018 – Afternoon

SESSION II: SMALL AND LANGE BOWEL

Chairman: Jimmy K. Limdi, *MB BS, FRCP (Lond & Ed), FEBGH, FACN, FACG (Manchester, UK)*

15:00 Diagnosis and Management of Small Intestine Bacterial Overgrowth
Luigi Gatta, *MD, PhD, FACG (Lido di Camaiore, Italy)*

15:30 Gluten Intolerance and Hypersensitivity: Beyond the Gluten Free Diet
Sheila E. Crowe, *MD, FACP, AGAF, FRCP (San Diego, CA, USA)*

16:00 NSAID-enteropathy: Diagnosis, Prevention and Treatment
Ángel Lanas, *MD, DSc, FACG, AGAF (Zaragoza, Spain)*

16:30 *Coffee Break*

17:00 Pathophysiology and Therapy of Functional Bowel Disorders
Focus on Irritable Bowel Syndrome
Giovanni Barbara, *MD, FRCP, FACG (Bologna, Italy)*

17:30 Diverticular Disease and Its Complications: from Guidelines to Clinical Practice
Neil H. Stollman, *MD, AGAF, FACP, FACG (Oakland, CA, USA)*

18:00 Management of IBD: What the Future Holds
Stephen B. Hanauer, *MD, FACG, AGAF (Chicago, IL, USA)*


Luigi Gatta

15:00 Diagnosis e Management of Small Intestine Bacterial Overgrowth

Luigi Gatta, MD, PhD, FACG

Consultant Physician & Gastroenterologist
Division of Gastroenterology & Digestive Endoscopy
Versilia Hospital, Lido di Camaiore, Lucca, Italy

The small bowel is responsible for approximately 90% of the overall energy absorption from the diet thanks to the large surface area of its mucosa [1, 2]. Indeed, it is the major site of nutrient digestion and absorption. The small intestine also acts as a primary source for producing important enteroendocrine hormones that regulate the initial phases of nutrient processing and digestion [3].

The proximal small bowel contains a low number of microorganisms, largely gram-positive aerobic, with rare facultative anaerobes, while the distal small bowel is a transition zone with the microbiota consisting mostly of facultative anaerobes and sparse populations of aerobic bacteria [4,5].

The normal enteric microbiota influences a variety of intestinal functions [6]. Unabsorbed dietary sugars are *recovered* by bacterial disaccharides, converted into short-chain fatty acids (and gases, such as hydrogen, methane, carbon dioxide and hydrogen sulphife), and used as an energy source by the colonic mucosa [7]. A wide range of vitamins (particularly those of the B group as well as vitamin K) and nutrients are produced by enteric bacteria [2]. Moreover, the relationship between the immune system and non-pathogenic microbiota is important in protecting the host from colonization by pathogenic species [3]. Finally, bacterial metabolism of some medications, such as mesalazine pro-drugs (like, for instance, sulphasalazine, olsalazine, balsalazide) within the intestinal lumen, is essential for the release of the active moieties [8].

Small intestine bacterial overgrowth (SIBO) arises when an increased number and/or abnormal type of bacteria (i.e. oropharyngeal or colonic type bacteria) occurs in the small bowel [4]. Therefore, SIBO represents an umbrella term, under which some different functional (e.g. irritable bowel syndrome, chronic constipation, diarrhoea) or organic (e.g. inflammatory bowel disease, coeliac disease, diverticular disease, etc.) conditions can be included, as – in each of them – bacterial proliferation (and consequent inflammation) may, at least in part, trigger similar abdominal symptoms [9].

The high concentration of bacteria interferes with normal small bowel nutrient absorption, and patients develop malnutrition and gastrointestinal (GI) symptoms

such as abdominal pain/discomfort, bloating, diarrhea, flatulence, steatorrhea and macrocytic anaemia, which can significantly impair quality of life [9]. Understanding of the importance of SIBO is being increasingly recognized, as evidenced by the number of publications over the years (Figure 1).

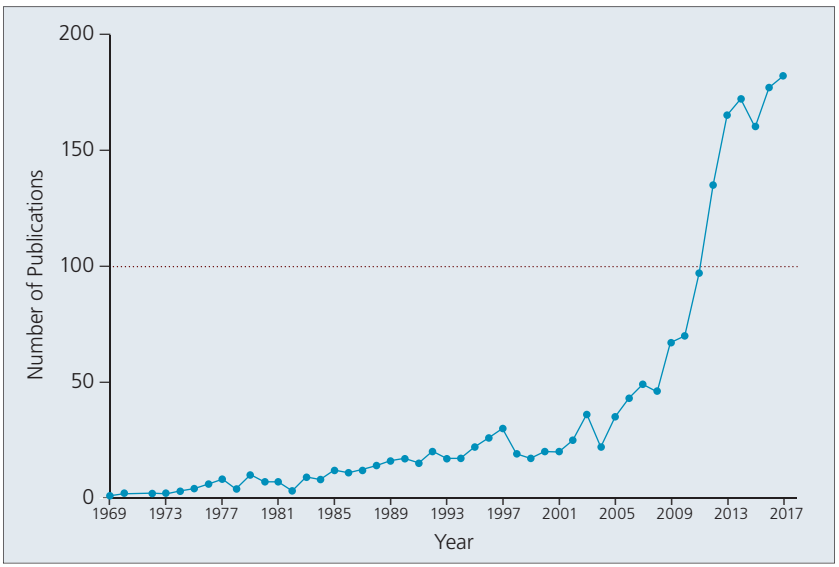

Figure 1: *Number of publications regarding SIBO in Medline and Embase*

Definition and Prevalence of SIBO

The idea that there could be an alteration of the *microbiota* of the small intestine was already suggested in the 19th century. Several studies performed between the 1950s and 1970s showed the consequences of this overgrowth or "contamination" in terms of B_{12} absorption, bile salt deconjugation, protein, carbohydrate and fat assimilation, and intestinal injury [10-14].

Historically, a bacterial concentration ≥10^5 colony forming units per milliners (CFU/ml) of aspirates from the small bowel was used to diagnose SIBO. However, many patients with a wide range of GI conditions and symptoms have increased bacterial counts in the small intestine compared with healthy controls, although total bacterial counts generally remain below 10^5 CFU/mL [15]. For these reasons, although there is no unanimous consensus, a bacterial concentration of >10^3 CFU/ml is nowadays considered significant of SIBO [16].

In addition to the absolute number of organisms, the variety of *microbiota* plays a *critical role* in the manifestation of signs and symptoms of overgrowth [17]. For example, a predominance of bacteria that metabolize bile salts to unconjugated or insoluble compounds may lead to fat malabsorption or bile acid diarrhoea. In contrast, microorganisms that preferentially metabolize carbohydrates to short chain fatty acids and gas may produce bloating, but not diarrhoea, since the metabolic products may be absorbed. Gram-negative coliforms, such as *Klebsiella* species, may produce toxins that damage the mucosa, interfering with absorptive function and causing secretion, thereby mimicking tropical sprue. As a consequence, some investigators have conceived the diagnosis of SIBO provided that the bacterial species, isolated in the jejunal aspirate, are those that normally colonize the large bowel (e.g., *Enterobacteriaceae*, e cocci, *Pseudomonas* spp., *Bacteroides* spp.) or that the same species are absent from saliva and gastric juice [4,9,18].

As there is no consensus for a definition for SIBO, its true prevalence and relationship with other clinical disorders remain uncertain. There are several reasons for this. Some patients may not seek medical care or SIBO may not be properly diagnosed by medical investigations [9]. SIBO might be asymptomatic or display non-specific symptoms only, and last but not least, all symptoms might be incorrectly ascribed to the underlying disease (leading to SIBO). A review has estimated that the prevalence of SIBO in healthy individual ranges between 0% and 20%, whilst, in several disease states, it can range between 5% and 92% (Table 1) [19]. Furthermore, diagnostic yield also depends on the methods used for investigation [15].

SIBO: Pathophysiology

SIBO develops when the normal homeostatic mechanisms that control enteric microbiota are disrupted (Table 2). Among the defensive factors, the two most important are gastric acid and intestinal motor activity. In the stomach, acid is able to impair the growth of most organisms entering from the oropharynx [4]. In the small bowel, the motility, particularly *via* phase III of the interdigestive migrating motor complex (MMC), help to limit the colonization of the small bowel by bacteria [4]. Other protective factors are represented by the integrity of the intestinal mucosa (including the mucus layer, defensins, immunoglobulins), the enzymatic and bacteriostatic properties of intestinal, pancreatic, and biliary secretions, the protective effects of the commensal microbiota, and the mechanical and physiologic properties of the ileocecal valve [4]. Although not always detected [20], SIBO may also result in microscopic mucosal inflammation, that contribute to symptoms by the loss of brush border enzymes (e.g., disaccharidases). This will determine presentation of more unabsorbed carbohydrates to intestinal bacteria for fermentation and it could also contribute to lactose intolerance [18]. Furthermore, the injury of the mucosa will increase intestinal permeability, which sets in motion a series of pathophysiology events, leading to the production of inflammatory cytokines that may add to damage and contribute to

Table 1: Reported prevalence of SIBO in disease states (from Grace *et al.* [19])

Miscellaneous		Dysmotility/ Gut wall Injury		Surgery		Neuromuscular Diseases	
Disease	Prevalence	Disease	Prevalence	Disease	Prevalence	Disease	Prevalence
Fibromyalgia	93%*	Coeliac Disease	9-67%	Bilateral Truncal Vagotomy	93%	Muscular Dystrophy	65%*
Chronic Pancreatitis	34-92%	Crohn's Disease	25-88%	Roux-en-Y Reconstruction	86%*	Parkinson's Disease	54%*
Chronic Fatigue Syndrome	81%*	Ulcerative Colitis	81%*	Abdominal Surgery	82%*		
IBS	4-78%	Non specific Dysmotility	76%*	Gastrectomy	63-78%		
PPI or H_2RA	26-75%	Connective Disease	43-55%	Ileocecal Valve Resection	32%		
Parental Nutrition	70%*	Hypothy-roidism	54%*				
Rosacea	46%*	Diabetes Mellitus	8-44%				
Liver Cirrhosis	17-36%	Radiation Enteropathy	26%*				
Obesity	17-41%						
End-stage Renal Failure	36%*						

* data based on one study only.

systemic complications [5]. It should be remembered that the paracellular route is the most important pathway for passive solute flow across the intestinal epithelial barrier, and its functional state depends on the regulation of the intercellular tight junctions [21]. Until recently, these structures were regarded as static. However, there are now several evidence showing that they are dynamic and readily adapt to a variety of developmental, physiological, and pathological settings [21]. Indeed, almost 20 years ago Fasano *et al.* [22] identified *zonulin* – a haptoglobin 2 precursor [23] – that it is able to modulate the permeability of tight junctions between cells of the gastroduodenal and small bowel wall [23]. *Zonulin* has been implicated in the pathogenesis of celiac disease and diabetes mellitus type 1 [21]. Recently, studies have also shown that this protein also triggers the increase of small bowel permeability during bacterial infection [24,25].

Table 2: Risk factors for development of SIBO

Failure of Gastric Acid Barrier	Failure of Small Bowel Clearance	Small Bowel Anatomic Alteration	Immuno-deficiency	Multifactorial
• Atrophic gastritis • Hypochlorhydria • Gastric bypass • Gastrectomy • Proton pump inhibitors	• Primary visceral neuropathy or myopathy • Connective tissue diseases (scleroderma, polymyositis) • Amyloidosis • Gastroparesis • Radiation enteropathy • Paraneoplastic syndrome • Medications (opioids, anticholinergics) • Idiopathic Intestinal pseudo-obstruction	• Short bowel syndrome • Small bowel diverticulosis • Small bowel strictures or fistulas • Small bowel obstruction • Blind loops (Roux-en-Y) • Ileocecal valve resection	• IgA deficiency • Combined variable immune deficiency • T cell deficiency	• Advanced age • Irritable bowel syndrome • Cirrhosis • Chronic pancreatitis • Obesity • Cystic fibrosis • Chronic renal failure • Celiac disease • Diabetes mellitus • Hypothyroidism • Tropical sprue • Intestinal failure

Reduced Gastric Acid

Gastric acid suppresses growth of ingested bacteria, thereby limiting bacterial counts in the upper small intestine. Diminished acid production (hypochlorhydria) is therefore a risk factor for SIBO [26]. A meta-analysis published in 2013, found that the OR of SIBO in proton pump inhibitor (PPI) users *vs.* nonusers was 2.28 (95% CI: 1.23 to 4.20) [27]. Interestingly, subgroup analysis revealed an association between SIBO and PPI use in studies that used duodenal or jejunal aspirate cultures to diagnose SIBO (OR: 7.58; 95% CI: 1.80 to 31.89), but no relationship was found in studies that used the glucose hydrogen breath test (GHBT) [27]. Even a second recently published meta-analysis found that the OR of SIBO in PPI users was increased (OR: 1.71; 95% CI: 1.20 to 2.43) [28]. However, in this case, Authors found that the association was present when the SIBO was diagnosed with either culture (OR: 2.22; 95% CI. 1.33 to 3.68) and GHBT (OR: 1.84; 95% CI: 1.03 to 3.30) [28]. An association between SIBO and H2 receptor antagonist have also been reported [29,30].

Motility Disturbances

Normal gastrointestinal motility involves a complex, tightly coordinated series of events designed to move material through the GI tract. During periods of fasting, a MMC develops every 90 – 120 minutes, working to sweep residual debris through the GI tract [31]. The current findings further support the concept that the MMC acts like an interdigestive *gastrointestinal housekeeper*, integrating mechanical (high phase III motor activity), physical (water secretion and "bile detergent"), biochemical

(acid and pepsin) and immunological (IgA) components into an effective "rinsing program" [32]. Several studies have demonstrated that abnormalities in the MMC may predispose to the development of SIBO [18]. This is the case of small bowel motility disorders, cirrhosis and portal hypertension as well as neuropathic (e.g. chronic intestinal pseudo-obstruction), or myopathic (e.g. scleroderma) processes. Impaired gastric peristalsis due to gastroparesis may lead to SIBO due to stasis of food and bacteria in the upper gastrointestinal tract.

In the past, the relationship between motility and the microbiota was viewed as unidirectional, with motility maintaining the sterility of the upper gastrointestinal tract and dysmotility predisposing to SIBO. It is now clear that this is a truly bi-directional relationship: not only can gut motor patterns influence the microbiota but changes in the microbiota can exert profound influences on gut sensorimotor function [33]. There are three main mechanisms whereby the microbiota could influence gut motor function [34]: 1) through the release of bacterial substances or end-products of bacterial fermentation, 2) *via* intestinal neuroendocrine factors and 3) indirectly, through the effects of mediators released by the gut immune response. An example of the interaction between these mechanisms is the so-called "ileal brake"[5]. Essentially, it consists of a slowing of proximal gut motility caused by passage of unabsorbed fat through the ileum liberating peptide YY, neurotensin, and glucagon-like peptide (Figure 2) [35,36].

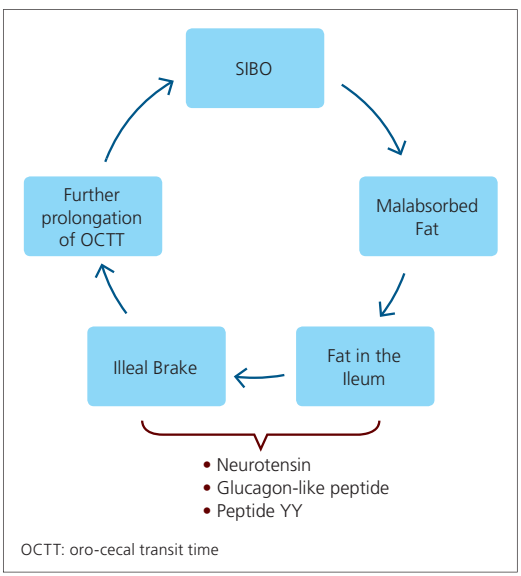

Figure 2: *How malabsorbed fat induces ileal brake while passing through the ileum, causing small bowel stasis and increasing bacterial overgrowth in the upper gut (from Ghoshal* et al. *[5])*

Other Predisposing Conditions

Structural abnormalities (be they congenital or acquired) in the GI tract represent an ideal environment for bacterial colonization and overgrowth [5]. Petrone *et al.*[37] reported that 82% of patients with SIBO and related symptoms (chronic abdominal pain, bloating, constipation and/or diarrhoea) had history of previous abdominal surgery. Patients who are immunodeficient, whether due to an abnormal antibody response or T-cell response, are prone to bacterial overgrowth. Patients with SIBO (compared to those with normal jejunal aspirates) were more likely to have abnormalities in intestinal mucosal immunity (evidenced by increased luminal IgA concentrations and lamina propria IgA plasma cell counts) [38]. SIBO can develop in a variety of patient populations, detailed in several reviews [4,19,26] to which the reader is referred.

Clinical Features

The clinical manifestations of SIBO are quite heterogeneous. They can range from vitamin B_{12} or iron deficiency in an asymptomatic individual to steatorrhea in surgical patients. Furthermore, SIBO is an important cause of otherwise unexplained diarrhoea in older patients, accompanied by weight loss, bloating, flatulence, and abdominal discomfort [4]. However, the classical features of SIBO are hardly seen today, with the possible exception of individuals with short bowel syndrome. This is probably due to the to the less frequent use of disabling surgical interventions, a better diagnosis and management of Crohn's disease, and an early diagnosis of celiac disease.

A 2013 retrospective study aimed to assess the overall yield of duodenal culture in patients referred for this test in an open access, high volume endoscopy centre at a major academic centre, and to identify symptoms, diagnoses and medications that are associated with SIBO in modern day practice [39]. Authors found that older age, steatorrhea and narcotic use were associated with SIBO (i.e. intestinal aerobic bacterial counts of more than 10^5 CFU/mL or intestinal anaerobic bacterial counts of more than 10^4 CFU /mL). Inflammatory bowel disease, small bowel diverticula and pancreatitis were also positively associated with an abnormal duodenal aspirate (defined as any bacterial growth of aerobic bacteria counts between more than 0 and less than 10^5 CFU/mL, or anaerobic bacterial counts between more than 0 and less than 10^4 CFU/mL).

Irritable Bowel Syndrome

SIBO can induce a wide range of clinical manifestations through effects on GI motility, visceral sensation, immune activation, carbohydrate digestion and absorption, bile acid metabolism, and intestinal epithelial permeability [4,5]. Being these mechanisms also implicated in the pathogenesis of irritable bowel syndrome (IBS) [17,40], the possibility of an association between SIBO and IBS is not surprising.

Indeed, in the last decade the role SIBO in the etiopathogenesis in IBS. It was initially showed that a positive lactulose hydrogen breath test (LHBT) was found in 78% of IBS

cases and that an antibiotic treatment leading to a negative LHBT determined a clinical improvement [41]. Afterwards, several studies have tried to understand if patients with IBS had more frequently SIBO. A meta-analysis published in 2009 found that the prevalence of SIBO in IBS ranged from 2% to 78%, depending from the type of test used to diagnose SIBO and from the diagnostic criteria used [42]. Studies have found that patients with IBS have higher bacterial counts in the proximal small intestine by quantitative culture than healthy controls [43,44], and patients with IBS are more likely than healthy volunteers to have an abnormal breath test [26,41,44,45].

There are several factors that are associated with SIBO among patients with IBS. A recent meta-analysis found that the pooled prevalence of SIBO in IBS was higher in female gender (OR 1.5; 95% CI: 1.0 to 2.1), older age (standard mean difference: 3.1 years, 95% CI: 0.9 to 5.4), and IBS-diarrhea (OR 1.7; 95% CI: 1.3 to 2.3) compared with other IBS subtypes. PPI use was not associated with SIBO (OR 1.1; 95% CI: 0.7 to 1.7) [46], confirming a result of a previous meta-analysis [42]. However, it still remains unclear if SIBO is a cause or a consequence of IBS. Indeed, it is possible that SIBO can cause IBS symptoms in some patients but, in others, alterations in motility, gut immune system, and microbiota could prompt to the development of SIBO [17].

Rifaximin has been broadly tested in this group of patients in order to evaluate its efficacy in symptom relief. TARGET 1 and TARGET 2 trials [47] randomized 1258 IBS patients without constipation to either placebo or rifaximin 550 mg thrice daily for 14 days. By week 4, there was an improvement in global IBS symptoms in the rifaximin group compared with the placebo group (40.7 vs. 31.7%; $p<0.001$), translating to a number needed to treat (NNT) of 11. Furthermore, a greater percentage of rifaximin randomized patients reported durable improvement in IBS symptoms during the 10-week follow-up period [47]. Recently, the TARGET 3 trial, designed to assess the safety and efficacy of repeated courses of rifaximin in individuals with diarrhoea-predominant IBS was published [48]. Of 2579 IBS patients receiving rifaximin, 41.6% showed clinical improvement within 4 weeks. Unfortunately, however, in all the TARGET studies [47,48], only few patients in some centers were tested for SIBO.

Diagnosis of SIBO

Culture

Traditionally, the direct aspiration and culture of jejunal fluid – with results expressed as colony forming unit per ml (CFU/mL) – although invasive, was regarded by many investigators as the *gold standard* for the diagnosis of SIBO [4,18]. Several techniques (including jejunal intubation under fluoroscopic guidance, endoscopically guided aspiration, mucosal brushing and even mucosal biopsies) have been used to obtain bowel contents for culture. These approaches are invasive, time-consuming and costly.

Moreover, aspiration-based approaches suffer from the potential for contamination of the aspirate with oro-esophageal flora (represented mainly by gram-positive bacteria) [5]. A critical issue is the choice of the cut-off to be used to define the SIBO. The concentration of bacteria in the gut increases from 10^3 – 10^4 CFU/ml in the duodenum and the jejunum, to 10^5 CFU/ml in the proximal ileum, to 10^5 - 10^8 CFU/ml in the terminal ileum, and 10^{10} – 10^{12} CFU/ml in the caecum [49,50]. SIBO was therefore usually defined as a total growth of $\geq 10^5$ CFU/ml [51,52]. However, this cut-off was obtained using highly symptomatic patients with high-risk conditions, while patients selected for testing often have no apparent risk factors for SIBO and frequently present non-specific symptoms [53]. Indeed, the North American consensus group endorsed a cut-off $>10^3$ CFU/mL for diagnosis of SIBO [16]. This recommendation was also based on a systematic review showing that the $\geq 10^5$ CFU/mL cut-off for conditions different from stagnant loop syndrome could be not valid [15]. Nevertheless, the use of a lower threshold level is prone to false positivity results.

A crucial issue is represented by the variety of *microbiota* that plays a *critical role* in the manifestation of signs and symptoms of overgrowth [17]. Therefore, some investigators have conceived the diagnosis of SIBO provided that the bacterial species, isolated in the jejunal aspirate, are those that normally colonize the large bowel (e.g., *Enterobacteriaceae*, e cocci, *Pseudomonas* spp., *Bacteroides* spp.) or that the same species is absent from saliva and gastric juice [4,9,18].

Breath Tests

Because of the drawbacks and limitations of the culture techniques, indirect tests were developed. Since they are non-invasive and less costly, these tests have become widely available and are currently used for the diagnosis of SIBO [4]. Hydrogen breath test [54] is based on the principle that bacterial metabolism of non-absorbed carbohydrates is the sole source of hydrogen and methane in exhaled breath (Figure 3). Therefore, after the oral ingestion of various substrates, hydrogen can be measured in exhaled breath [55]. The lactulose hydrogen breath test (LHBT) and the glucose hydrogen breath test (GHBT) are the most widely used in clinical practice [55].

Lactulose is a synthetic, nonabsorbable disaccharide (fructose and galactose) that is not absorbed by the small intestine mucosa. In the cecum it is metabolized by colonic bacteria to short-chain fatty acids and gases including hydrogen and/or methane. If SIBO is present, the proximally displaced bacteria theoretically should determine an early increase in breath hydrogen excretion [56]. In the classic description of this test, a second increase in breath hydrogen excretion should also occur as a consequence of the fermentation of lactulose in the cecum. However, this "double-peak" pattern of breath hydrogen or methane excretion is the exception rather than the rule [55]. During the time, a variety of end points have been used to define a positive test. Recently, the North American Consensus for hydrogen and methane-based breath

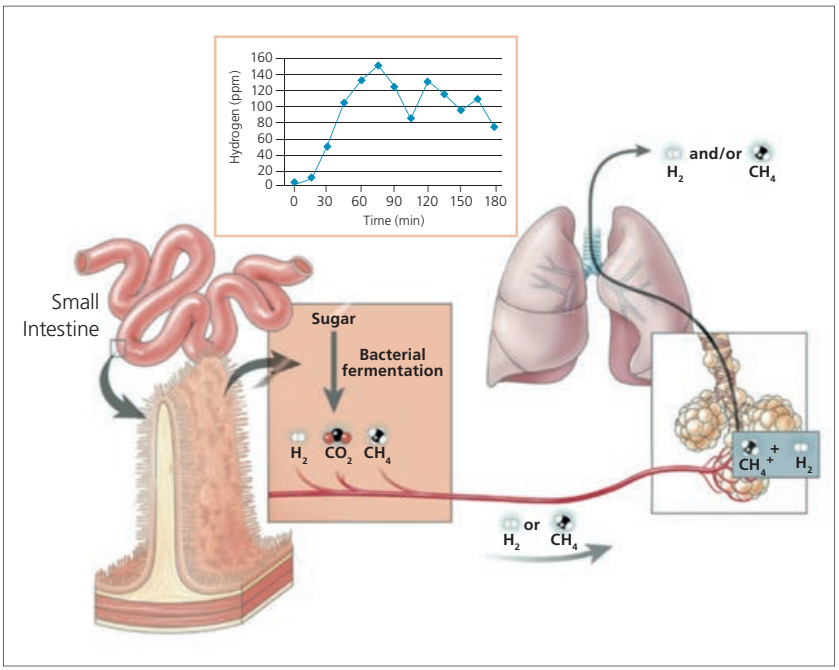

Figure 3: *Principle of hydrogen breath tests. After carbohydrate fermentation by colonic anaerobic bacteria, H_2 gas is produced, which diffuses into the body and is excreted in the expired air through the lungs. The insert shows a typical tracing of a "double peak" LHBT in a patient with SIBO (from Saad & Chey [55])*

testing in gastrointestinal disorders suggested that *until better data are available, for clinical and research purposes, a rise of ≥20 part per million (ppm) from baseline in hydrogen by 90 min should be considered a positive test* [16]. For LHBT, the sensitivity in clinical trials ranges from17% to 68%, while the specificity from 44% to 86% [55].

Because ingested lactulose is non-absorbed, it theoretically should be able to detect bacterial fermentation *anywhere along the length of the small intestine*. However, rapid transit, as may be found in some SIBO-associated conditions (e.g. IBS), makes interpretation of the test even more difficult since lactulose itself (even at low doses) does accelerate intestinal transit [57]. As a consequence, providers who choose the LHBT should accept a higher rate of false-positive test results. Indeed, Yu *et al.* showed

that when lactulose breath test was combined with orocecal ^{99m}Tc-scintigraphy, the time of increase in breath hydrogen levels corresponded with an increase in accumulation of ^{99m}Tc in the cecum in 88% of cases, suggesting a high rate of false positive results [58]. Similar results have been found by other investigators [59,60].

Glucose is a monosaccharide that is completely absorbed in the proximal small intestine under normal conditions. However, when SIBO is present, glucose is metabolized by bacteria before it can be absorbed. Usually, a single peak in the hydrogen concentration after the ingestion of glucose is indicative of SIBO [55]. Similar to the LHBT, there is no widely agreed upon standard for the performance or interpretation of the GHBT. An increase ≥ 20 ppm over baseline is recommended by the North American consensus group [16,18], although an increase greater than 10 to 12 ppm from baseline has been suggested from the Rome Consensus Conference [61]. For GHBT, the sensitivity in clinical trials ranges from 20% to 93%, while the specificity from 30% to 86% [55].

As glucose is absorbed primarily in the proximal small bowel, it may not detect SIBO occurring in more distal sections of the small bowel. Therefore, providers who choose the GHBT should accept an higher rate of false-negative test results [55]. Nevertheless, Lin *et al.* found that, when scintigraphy was used to determine whether the hydrogen (or methane) increase occurred before or after the glucose bolus arrived at the cecum, almost half of the patients evaluated had an abnormal GHBT after the arrival of the head bolus, suggesting, even in this case, a high rate of false positive results [62]. Nevertheless, both for the LHBT and GHBT, there are conflicting opinions whether the arrival of a small portion of the overall radiolabelled material in the colon [58,62] proves that the fermentation is from colonic rather than small bowel bacteria [63,64].

In addition to hydrogen, methane can also be measured in the exhaled breath. The addition of methane to hydrogen measurement is believed to improve the diagnostic accuracy by capturing from 20% to 30% of patients who harbour bacteria producing methane as a main product of metabolism of carbohydrates [65]. Thus, the measurement of breath methane in addition to hydrogen can improves the sensitivity of the test. The North American consensus group recommends that an increase in breath methane ≥ 10 ppm should be used as an additional criterion diagnostic of SIBO [16]. However, even if methanogenic bacteria seem to be present in the majority of human beings, only those with a critical concentration of such bacteria produce measurable levels of methane [66].

Finally, it remains unclear how to interpret breath tests with no hydrogen or methane production, a not infrequent occurrence. This may occur because of the presence of bacteria in the gut, producing predominantly hydrogen sulphide, which cannot be easily measured by currently available techniques [18]. However, new apparatuses able to measure all the three gases have been developed and are being validated.

Management of SIBO

Induction of Remission

The primary aim of the management of SIBO should be the treatment or correction of any underlying disease or defect, whenever possible. Unfortunately, several of the clinical conditions associated with SIBO, like, for instance, post-surgical GI abnormalities or neuropathies/myopathies, are irreversible. Drug-induced SIBO could be, however, ameliorated via the elimination of the given medication (e.g. PPIs) or substitution with a less harmful one. Bacterial overgrowth must be, of course, eliminated and any associated nutritional deficiency duly corrected [18]. Eradication of SIBO is based on antibiotic therapy. Its objective should not be to eradicate the entire bacterial flora but rather to modify the intestinal microecology in order to get symptom relief. Although, ideally, the choice of antimicrobial agents should reflect in vitro susceptibility testing, this is usually impractical because many different bacterial species, with different antibiotic sensitivities, typically coexist. In a study where jejunal samples of 63 consecutive patients with diarrhoea and malabsorption were cultured, the mean number of bacterial genera was 4.6±0.8 [67]. The main bacteria recovered were *Streptococcus* (71%), *Escherichia coli* (69%), *Staphylococcus* (25%), *Micrococcus* (22%), *Klebsiella* (20%), *Proteus* (11%) for microaerophilic bacteria, and *Lactobacillus* (75%), *Bacteroides* (29%), *Clostridium* (25%), *Veillonella* (25%), *Fusobacterium* (13%), and *Peptostreptococcus* (13%) for anaerobic bacteria. Effective antibiotic therapy must therefore cover both aerobic and anaerobic enteric bacteria.

Although seldom used in clinical practice, antimicrobials, whose activity is limited to anaerobes, such as metronidazole or clindamycin, have a limited role as monotherapy. Different drugs (and different dosages) with a success rate ranging from 30% to 100% have been employed [68,69]. Unfortunately, after successful eradication SIBO does recur in a dose-dependent fashion, with more than 40% of patients displaying again a positive GHBT after 9 months [70]. All GI symptoms increased in parallel with SIBO recurrence. Older age, history of appendectomy and chronic PPI use were significantly associated to GHBT positivity recurrence. Due to the relapsing nature of this condition, serval courses of antimicrobial therapy are often needed. The potential of adverse effects and drug resistance associated with long-term antimicrobial treatment are obviously a cause for concern. The availability of poorly absorbed antibiotics (like rifaximin) has been a significant advancement in the therapy of SIBO and has stimulated a number of RCTs in order to establish the best regimen (drug, dose and duration) for a successful eradication.

Rifaximin

Rifaximin (4-deoxy-4′-methylpyrido(1′,2′-1,2)imidazole (5,4-c)rifamycin SV) is a product of synthesis experiments designed to modify the parent compound, rifamycin, in order to achieve low GI absorption while retaining good antibacterial activity [71].

Both experimental and clinical pharmacology have clearly shown that this compound is a non-systemic antibiotic with a broad spectrum of antibacterial activity, covering Gram-positive and Gram-negative microorganisms, both aerobes and anaerobes [72]. Being virtually non-absorbed, its bioavailability within the GI tract is rather high, with intraluminal and faecal drug concentrations largely exceeding the *in vitro* minimum inhibitory concentrations (MICs) estimated against a wide range of pathogenic enterobacteria. The GI tract represents therefore the primary therapeutic target and GI infections the main indication. This antibiotic has therefore little value outside the enteric area, and this will minimize both antimicrobial resistance and systemic adverse events. Indeed, the drug has been proven to be safe in all patient populations, in the short-term and long-term (up to 6 months of continuous use) [72,73], and in young children [74].

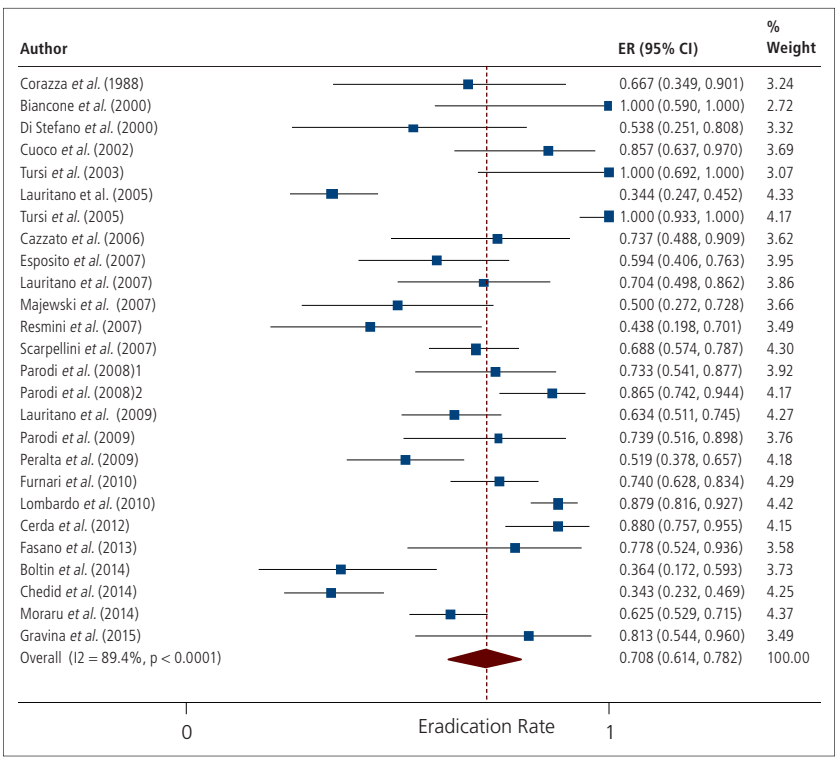

Figure 4: *Forest plot of pooled eradication rate of rifaximin in SIBO according to the ITT analysis (from Gatta & Scarpignato [75])*

A recent meta-analysis aimed to summarize evidence about the efficacy and safety of rifaximin to eradicate SIBO in adult patients [75]. Thirty-two studies involving 1331 patients were included: the overall eradication rate according to *intention-to-treat* and *per protocol analysis* were 70.8% (95% CI: 61.4 to 78.2) (Figure 4) and 72.9% (95% CI: 65.5 to 79.8), respectively. Meta-regression showed that eradication significantly increased for unit increase in dosage of rifaximin (Figure 5), in non-RCTs, and in studies where fibres, mesalazine, pre- or probiotics were concomitantly used with rifaximin [75].

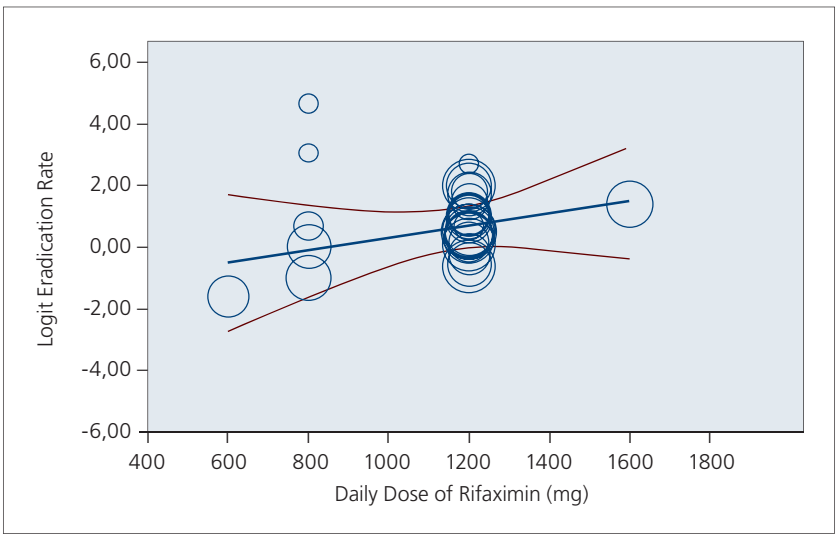

Figure 5: *Meta-regression plot: Logit of Eradication Rate versus Daily Dose of Rifaximin, adjusted for all the other covariates evaluated (from Gatta & Scarpignato [75])*

When patients with IBS were evaluated, the pooled eradication rates were 71.6% (95% CI: 56.7 to 84.4) (Figure 6) and 75.4% (95% CI: 65.0 to 84.5), according to the *intention-to-treat* and *per protocol analysis*, respectively. In two comparative studies, rifaximin (1200 mg for 7 days) was compared to chlortetracycline (333 mg t.d.s for 7 days) [76] or metronidazole (750 mg/die for 7 days)[77], respectively. According to *intention-to-treat* analysis, the overall eradication rate was 61.6% (95% CI: 51.1 to 71.6) and 37.6% (95% CI: 21.1 to 55.6) in patients randomized to rifaximin and other antimicrobials respectively, with a difference in eradication rate of 24% (95% CI: 6.2 to 35.5) in favour of rifaximin [75].

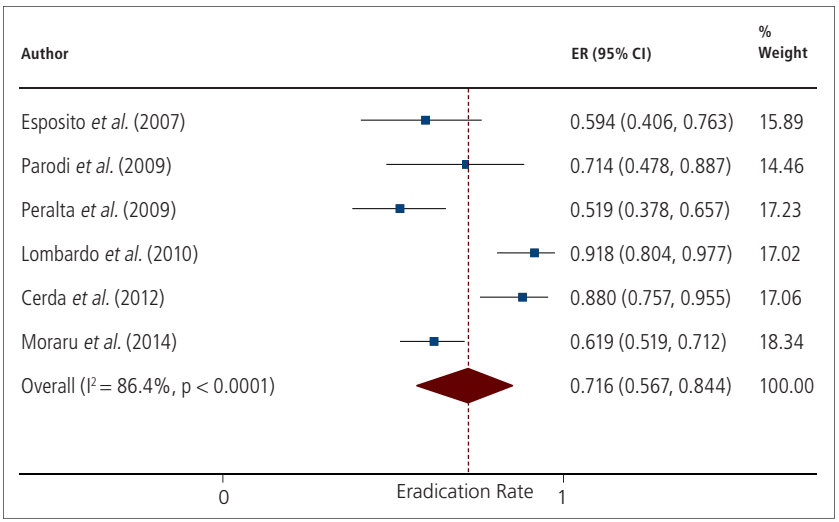

Figure 6: *Forest plot of pooled eradication rate of rifaximin in patients with IBS and SIBO according to the ITT analysis (from Gatta & Scarpignato [75])*

The evaluation of studies assessing symptoms before and after treatment with rifaximin showed that different symptoms were measured in different ways. A thorough analysis of these studies pointed out that symptoms improved after therapy in a large proportion (≥75%) of trials, an effect seen more frequently in studies including IBS patients [75]. The overall rate of adverse events was 4.6% (95% CI: 2.3 to 7.5). Meta-regression and sub-group analysis revealed that non-RCTs presented a significant lower incidence of AEs, when compared to RCTs [75].

Probiotics

The role of probiotics in the management of SIBO remains to be elucidated. Indeed, the concept of replacement of microbiota in the treatment of SIBO is intriguing, yet the data on efficacy of probiotics in treatment of SIBO, are scanty [78].

The meta-analysis performed to evaluate the effectiveness of rifaximin to eradicate SIBO [75], identified one study where SIBO positive patients were treated with rifaximin followed by a cycle of probiotics (*Lactobacilli* and *Bifidobacteria* based preparation) for twenty-day. Follow-up was performed 4–5 months after the end of treatment and revealed an eradication rate of 82.6% (95% CI: 61.2-95) [79].

A recent meta-analysis [80] identified 9 studies where probiotics were used to eradicate SIBO: 7 studies used probiotics alone, and 2 studies used probiotics with antibiotics. The pooled eradication rate was 53.2% (95% CI: 40.1% to 65.9%) for probiotics alone and 85.8% (95% CI: 69.9% to 94.0%) for probiotics *plus* antibiotics. Five RCTs were also available for meta-analysis, including 2 trials comparing probiotics with metronidazole, 2 trials comparing probiotics with placebo, and 1 trial comparing the probiotics plus minocycline with minocycline alone. Taken together, the results suggested that patients with SIBO using probiotics had a significantly higher SIBO decontamination rate compared with the non-probiotic users (RR=1.61; 95% CI: 1.19 to 2.17) [80]. Though, authors recommended to perform prospective large, well-designed clinical trial to confirm their findings.

Elemental Diet

For patients with allergies to antibiotics or do not respond to antibiotics, therapeutic options are quite limited. Elemental diet liquids contain nutrients in an easily digestible form, and typical formulations include essential and non-essential amino acids, simple carbohydrate, vitamins (fat- and water-soluble), minerals, electrolytes, and small amount of fat (less than 1%). These diets are believed to be absorbed within the first few feet of small bowel and potentially limiting the delivery of nutrients to the bacteria residing in distal portion of small bowel [81,82,83]. For these reasons, these formulations may be a safe and effective alternative to antibiotics [78]. In a retrospective study, 124 patients with methane- or hydrogen-predominant SIBO were treated exclusively with elemental diet (Vivonex™ Plus, Novartis Nutrition Corp., Minneapolis, MN) for at least 2 weeks. If breath test did not normalize by week 2, patients continued the diet for a total of 3 weeks. Fourteen patients could not tolerate the diet and dropped out. By day 15, 80 % of subjects normalized their breath test. Of 19 subjects who did not normalize their breath test, only five had a normal breath test by day 22 for a cumulative response of 85 %. Patients who normalized their breath test showed 66 % improvement in symptoms as opposed to 12 % improvement in patients with persistently abnormal breath tests [84]. While the cost and palatability of elemental formulations can be a limiting factor in their use, this strategy may be effective in the induction of remission of SIBO and deserves specifically-designed randomized clinical trials.

Herbal Antibiotics

Traditionally, a number of herbs have shown antimicrobial activity [85]. It has been suggested that the use of plant extracts with antimicrobial activity would be as effective as antibiotic therapy for patients affected by SIBO. In a non-randomized controlled trial, 37 patients with SIBO received herbal therapy, and 17 (46%) had a negative follow-up LHBT. No data was provided regarding clinical response [86]. Although the use of herbal medications with antimicrobial properties such as peppermint oil in the treatment of SIBO is interesting [87], these compounds need to

undergo robust clinical trials for assessment of their efficacy, correct dosing, and safety profiles before widespread clinical use.

Miscellanea

The predominant methane-producing bacteria in the gut, *Methanobrevibacter smithii*, are resistant to many antibiotics [18]. Therefore, antibiotic monotherapy is probably insufficient in these patients. It was showed that a combination of rifaximin and neomycin was more effective than either antibiotic alone in methane-producers [88]. Of the subjects receiving the treatment of rifaximin and neomycin, 85% had a clinical response, compared with 63% of subjects in the neomycin only group, and 56% of subjects in the rifaximin only group. When evaluating methane eradication results, 87% of subjects taking the rifaximin and neomycin combination eradicated SIBO, compared to 33% of subjects in the neomycin, and only 28% of subjects in the rifaximin [88]. Nevertheless, it should be emphasized the sample size of the study was small. Recently, there has been interest in use of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (i.e. drugs belonging to the statin class) as possible treatment of methane-positive SIBO [89]. Statins have been shown to inhibit methane production by an effect on cell biosynthesis and by directly interfering with methanogenesis [90]. However, whether this translates into a meaningful clinical benefit requires further studies.

Maintenance of Remission

SIBO is a relapsing condition, especially when there are predisposing factors [78]. In a study, 80 consecutive patients affected by SIBO and decontaminated by rifaximin were reassessed at 3, 6, and 9 months after evidence of GHBT normalization [70]. Authors found that 13, 28, and 44% of SIBO patients experience a relapse of their symptoms and breath test positivity at 3, 6, and 9 months after induction of remission with rifaximin, respectively. Therefore, following induction of remission, one should consider implementing appropriate therapeutic interventions to decrease the chance of recurrence (i.e., maintenance of remission).

Watchful Observation and Retreatment as Needed

Watchful observation is a reasonable option after induction of remission of SIBO, although most experts believe that patients will eventually relapse [78]. In the TARGET -3 study [48], 36 % of responders in the open phase did not experience a relapse for at least 22 weeks after treatment with rifaximin. Moreover, almost one third of patients who relapsed after open-label therapy responded to retreatment with rifaximin. Even if no patient was tested for SIBO in this study, it should be clinically reasonable, for those patients who are a higher risk of relapse, a strictly observation and eventually a plan for maintenance of remission.

Use of Prokinetic Agents

These compounds could theoretically be able to restore the impaired GI motility, which represent an important defensive factor against bacterial colonization [32]. Therefore, prokinetics drugs such as motilin receptor agonists (e.g., erythromycin and azithromycin) and 5-HT_4 agonists (e.g., tegaserod, cisapride, and prucalopride) can induce phase III MMCs in a fasting state [91] and potentially decrease the recurrence of bacterial overgrowth. In patients with cirrhosis, adding cisapride to antimicrobial treatment during a 6-month period significantly improved fasting cyclic activity, reduced the duration of orocecal transit time, and decreased SIBO while placebo was ineffective [92]. In patients with scleroderma, who had no spontaneous migrating complexes, octreotide (100 µg subcutaneously) induced 3.6±2.3 complexes every three hours. Treatment with a low-dose (50 µg every evening) octreotide for three weeks reduced GHBT and improved symptoms (nausea, bloating, and abdominal pain and, albeit less, vomiting) [93]. Erytrhomycin (a motilin agonist) and tegaserod (a 5-HT_4-partial agonist) were found to be capable of delaying recurrence of SIBO after successful eradication [94]. The number of symptom-free days was significantly higher with tegaserod (Figure 7), which, however, in 2007 was withdrawn from the market [95].

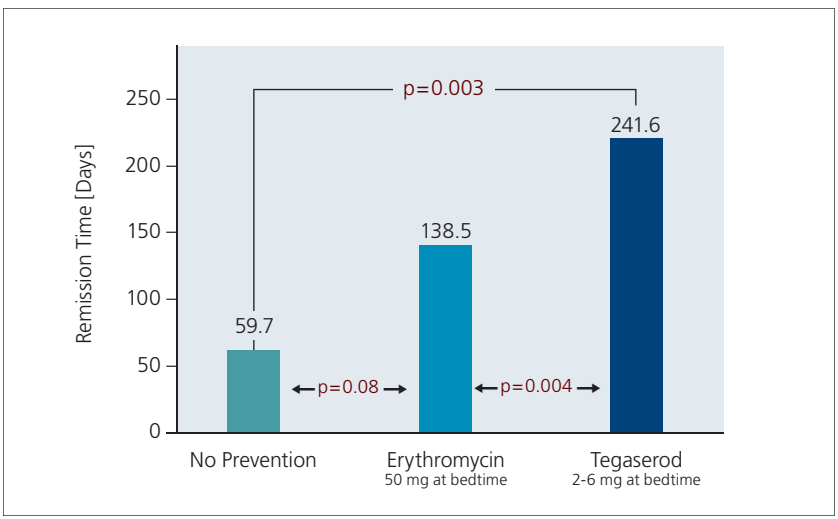

Figure 7: *Symptom-free days in patients with SIBO, successfully eradicated, to whom erythromycin (N=42, 50 mg at bedtime), tegaserod (N= 26, 2-6 mg at bedtime) or no treatment (N=6) have been given (From Pimentel* et al. *[94])*

Diet Restriction

A low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet significantly affects the gut microbiota [96]. However, to date, no study has systematically addressed the role of diet in SIBO patients. Carbohydrate intolerance (e.g., lactose, fructose, and fructan) is quite common among SIBO patients [97], and dietary restrictions could lead to symptomatic improvement. From a theoretical point of view, a diet with low fermentable foods could decrease the chance of bacterial overgrowth by creating a less favor luminal environment for overgrown bacteria [78]. A systematic review found that a low FODMAP diet improved overall IBS symptoms in 6/6 trials, but the key principle in its success was dependent on dietary education [98]. Overall, dietary education and avoidance of fermentable foods could have favorable effects on symptom control. Nevertheless, the role of dietary intervention in objective outcomes of induction and maintenance of treatment of SIBO needs further evaluation.

Conclusions

SIBO is a challenging clinical condition. Its aetiology is usually complex and multifactorial and the syndrome is often misdiagnosed and generally under-diagnosed. Clinical symptoms may be subtle and non-specific, which makes diagnosis difficult without objective testing. Nevertheless, SIBO can cause severe malabsorption, serious malnutrition and deficiency syndromes. In front of predisposing factors, many of which are unmodifiable, therapy is palliative and prognosis usually serious.

The recent discovery of an association between SIBO and functional gut symptoms, albeit controversial, has renewed interest in this mimicry. SIBO represents indeed an umbrella term, under which some different functional (e.g. IBS, chronic constipation, diarrhoea) or organic (e.g. IBD, celiac disease, diverticular disease, etc.) conditions can be included, since – in each of them – bacterial proliferation may, at least partially, trigger symptoms. On these grounds, the availability of poorly absorbed antimicrobials (i.e. rifaximin) has been an advance in treatment, which needs to be refined to identify the best dose and duration to maximize eradication and prevent recurrence. The global management of patients with SIBO will be, however, multifactorial (including nutritional support and dealing with the underlying abnormalities) and long-term.

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CURRENT AND FUTURE
MANAGEMENT OF DIGESTIVE
DISEASE: FROM BENCH TO BEDSIDE

Notes


Sheila E. Crowe

15:30 Gluten Intolerance and Hypersensitivity: Beyond the Gluten Free Diet

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Food Allergies and Intolerances: Focus on Wheat and Gluten Disorders

Up to 20 percent of the general population in the USA and more than half of the patients with irritable bowel syndrome (IBS) report recurrent adverse reactions to specific food(s) or food group(s). There is an increasing number of the USA population, who avoid wheat due to celiac disease (1% in the USA) and similar frequency in most populations that bear HLA DQ2/8 genes [1]. The remainder of a large group of reactions to foods are referred to as food intolerances. Although most patients refer to their reactions as an "allergy", the vast number of adverse reactions to food are not based on any known immunological reaction. Such non-immunological adverse food reactions to foods (ARF) arise from physiological, metabolic diseases, toxin-mediated reactions, gastrointestinal infections, deficiency of digestive enzymes and disorders, resulting from many anatomic and neurologic abnormalities (Table 1).

Table 1: Categories of sensitivities or intolerances to food

Category	Examples
Food toxicity	Effects of food-borne pathogens, including microbial toxins
Pharmacological	Adverse reactions to histamine in foods, such as scombroid fish poisoning
Metabolic	Lactose intolerance
Physiological	Consequences of ingestion or digestion of certain foods, such as fatty foods, legumes, and many other foods
Psychological	Eating disorders, aversion to food because of taste, texture, and other mechanisms
Idiosyncratic	Unpredictable and unexplained reactions to foods; e.g., nonceliac gluten sensitivity

Patient Cases

1 – A Case of Gluten Sensitivity

- A 58-year old woman with abdominal bloating and discomfort after eating various foods, abdominal cramping and loose stools (ranging from 2 to 3 per day), without blood for the past few years. Symptoms are relieved by passage of stool
- She attended a San Diego Celiac Support Association meeting and comes to my clinic concerned that she has celiac disease
- No family or personal history of allergic/atopic disorders or autoimmune disease
- She went on a gluten free diet (GFD) two months ago. She feels better but reports that she is allergic to onions and peppers since these cause bloating, pain and loose stools. She wants to know what she should eat and what not to eat

How do you respond to the patient and what is the diagnosis?

2 – Another Case of Gluten Sensitivity

- 25 year-old male, who is generally healthy with some symptoms
- He requests a 2nd opinion consult for gluten sensitivity
- Bloating & foggy mind with gluten for 3 years
- No family or personal history of atopy or autoimmune conditions
- Saw a naturopath, purchased supplements and vitamins
- Started a GFD after the following testing (he paid out of pocket)
- Uncertain what he should eat

Test results from Case 2

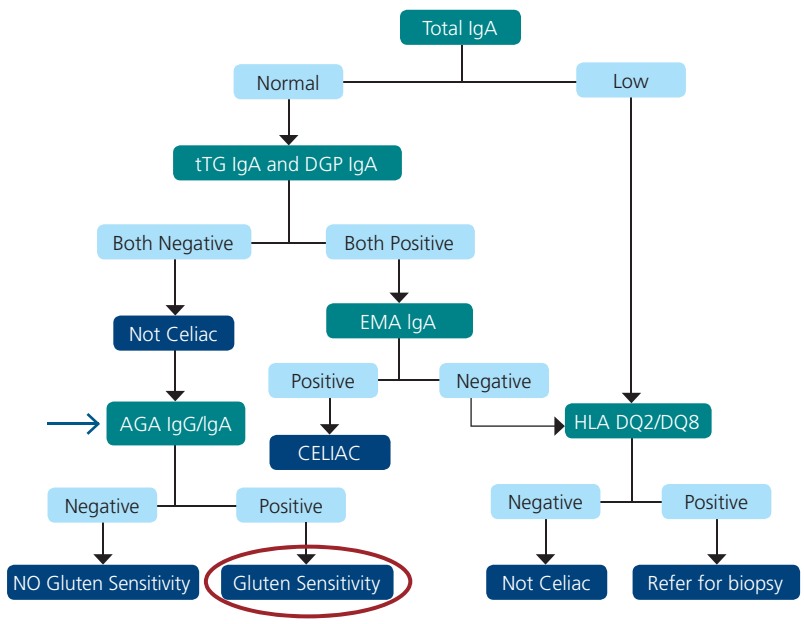
TEST		RESULT			
	Array 3 – Wheat/Gluten Proteome Reactivity & Autoimmunity	In range (Normal)	Equivocal*	Out of range	Reference (ELISA Index)
→	Wheat IgG		1.33		0.3-1.5
	Wheat IgA	0.43			0.1-1.2
	Wheat Germ Agglutinin IgG	0.64			0.4-1.3
	Wheat Germ Agglutinin IgA	0.39			0.2-1.1
	Native Deamidated Gliadin 33 IgG	0.68			0.2-1.2
	Native Deamidated Gliadin 33 IgA	0.28			0.1-1.1
→	Alpha Gliadin 17-mer IgG		1.14		0.1-1.5
	Alpha Gliadin 17-mer IgA	0.43			0.1-1.1
→	Gamma Gliadin 15-mer IgG		0.43	1.84	0.5-1.5
	Gamma Gliadin 15-mer IgA	0.26			0.1-1.0
	Omega Gliadin 17-mer IgG			1.43	0.3-1.2
	Omega Gliadin 17-mer IgA	0.40			0.1-1.2
	Gliadin 21-mer IgG	0.57			0.1-1.5
	Gliadin 21-mer IgA	0.33			0.1-1.3
	Gluteomorphin + Prodymorphin IgG	0.96			0.3-1.2
	Gluteomorphin + Prodymorphin IgA	0.26			0.1-1.2
	Gliadin-Transglutaminase Complex IgG	0.59			0.3-1.4
	Gliadin-Transglutaminase Complex IgA	0.48			0.2-1.5
→	Transglutaminase-2 IgG			1.61	0.3-1.6
	Transglutaminase-2 IgA	0.58			0.1-1.6
	Transglutaminase-3 IgG	0.59			0.2-1.6
	Transglutaminase-3 IgA	0.26			0.1-1.5
	Transglutaminase-8 IgG	0.78			0.2-1.5
	Transglutaminase-8 IgA	0.62			0.1-1.5
	Array 2 – Intestinal Antigenic Permeability Screen	In range (Normal)	Equivocal*	Out of range	Reference (ELISA Index)
	Actomyosin IgA**	7.43			0.0-20
	Occludin/Zonulin IgG	0.33			0.2-1.5
	Occludin/Zonulin IgA	0.22			0.1-1.8
	Occludin/Zonulin IgM	1.11			0.1-2.1
	Lipopolysaccharides (LPS) IgG	0.68			0.1-1.6
	Lipopolysaccharides (LPS) IgA	0.13			0.1-1.8
	Lipopolysaccharides (LPS) IgM	1.13			0.1-2.0

Test results from Case 2 – Celiac & Gluten Sensitivity

Immunologic Markers			
Biomarker	**Result**	**Serum Immunologic Markers**	**Reference Range**
Total IgA	319	[Sufficient]	62.0-343.0 mg/dl
Anti-transglutaminase IgA	12	[Negative]	<=4 U/mL
Anti-deamidated Gliadin IgA	6	[Negative]	<=20 U/mL
→ Anti-gliadin IgA	29	[Weak Positive]	<20 U/mL
Anti-gliadin IgG	11	[Negative]	<20 U/mL

Interpretation

Patient results are consistent with Possible Gluten Sensitivity. Clinical correlation advised.



In Europe and North America the term "food allergy" comprises disorders that arise from an abnormal immunological reaction to food [2]. In this review, case studies of wheat-related disorders are presented in order to demonstrate the key differences between food allergy and intolerance, and to discuss the approach to their diagnosis and treatment. Wheat is a good example of a food that can be an allergic disorder based on IgE (wheat allergy mainly in childhood and rare in adult life). In contrast, celiac disease, is a T cell-mediated immune reaction to wheat proteins, gluten and gliadin that requires the host to have HLA-DQ2/8 genes and leads to a disease of the small intestine and in some cases also a skin disorder, dermatitis herpetiformis (DH). More recently, a new disorder, eosinophilic esophagitis (EoE), has been increasing in prevalence in the USA, Europe, and many advantaged countries [3]. Amongst other common foods soy, eggs, and cow's milk, wheat can drive this eosinophilic inflammation in the esophagus [4,5].

Another important food intolerance in the USA and other economically advantaged regions of the world is a reaction to a group of foods including fructose, oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP), first reported and named by Susan Shepherd, RDN in Australia [6]. Milk sugar (lactose) is a very common cause of food intolerance around the world due to a genetically programmed down regulation of lactase levels such that many individuals world-wide have lactose intolerance, developing in later childhood and throughout adult life. However, a rare congenital lactase genetic disorder can be fatal if not recognized due to the absence of lactase. Other sugars and starches comprise FODMAPs. For example, a new wheat disorder is an intolerance that arises from wheat starch which comprises fructans/fructose and many patients have wheat-induced symptoms that can mimic symptoms of celiac disease. The importance of FODMAPs is illustrated by the recent study implicating fructans, not gliadins, in the pathogenesis of gluten intolerance [7]. Interestingly, many patients with celiac disease develop other symptoms due to starches (rice, corn, soy, buckwheat, etc.,) that are associated with non-gluten proteins in gluten-free foods. Data indicate increased amounts of wheat are ingested annually around the world. Understanding wheat allergy and other wheat related disorders is important to help patients with their dietary disorders [8].

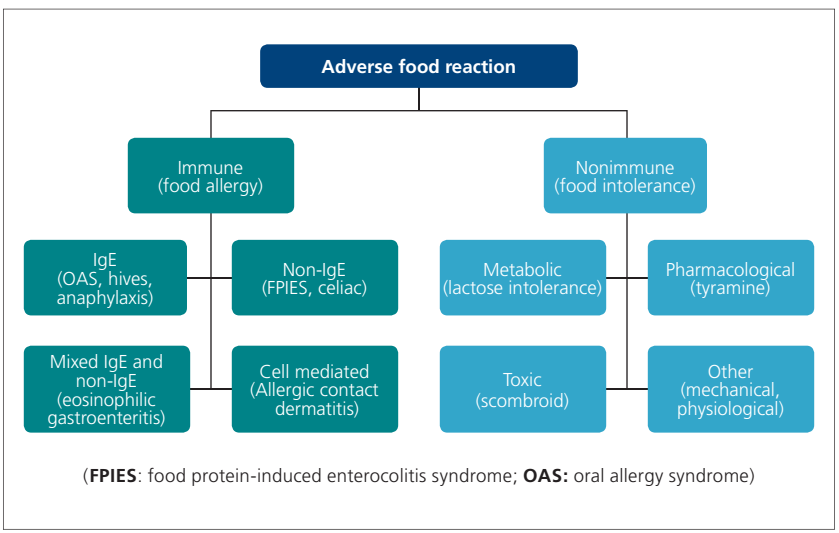
It is known that placebo responses are frequent, up to 70% in IBS. It has been known for many decades that gluten (with increased prolamines) is hard to digest, with an increase in stool volume. When patients are on a gluten free diet they often eliminate other dietary factors – fast food, processed foods and also avoid wheat starch. One Italian study reported symptom improvement after gluten withdrawal for celiac disease but its positive predictive value (PPV) that was only 36% [9].

Food Allergies and Intolerances: Epidemiology

It is estimated that up to 20% of the population has experienced adverse reactions to specific foods or food groups [10]. More than one-half of the patients with IBS report symptoms associated with certain foods [11]. The majority of the adverse food reactions is not immunological and is not life-threatening. These are referred to as food intolerances. In contrast, food allergy is an abnormal immunologic response following consumption of a food, which can be potentially life-threatening. It is less common than food intolerance, and the prevalence of IgE-mediated food allergy is estimated to be 1-2% in adults and less than 10% in children [12].

Food Allergies and Intolerances: Etiology/Pathogenesis

While food allergy is an abnormal immune response to an ingested food, food intolerance does not arise from immune system dysregulation. Food intolerance is a nonallergic adverse food reaction (AFR) that can be caused by a variety of disease processes, including intolerance of foods containing FODMAPs, gastroesophageal reflux disease (GERD), gastrointestinal infections, disorders resulting from structural and functional abnormalities (e.g. gallbladder disease, pancreatic insufficiency), metabolic diseases and toxin-mediated reactions (Figure 1) [13].



(**FPIES**: food protein-induced enterocolitis syndrome; **OAS:** oral allergy syndrome)

Figure 1: *Classification of adverse food reaction (from Leung & Crowe [13])*

Food allergy results from a breakdown of immunologic tolerance to a food. It is often categorized based on the immune pathway leading to the breakdown leading to IgE-mediated, non-IgE mediated, or mixed IgE/non-IgE-mediated. There has been an apparent increase in the prevalence of food allergy in the recent years which cannot be explained by genetics alone. Several hypotheses have been advanced to explain the role of specific environmental factors, and their respective supporting evidence were summarized in a recent report published by the National Academies of Sciences, Engineering and Medicine and reviewed by Sicherer and Simpson [14].

Development of an IgE-mediated allergic reaction is a multi-step process at the molecular level, with the involvement of several cell types. When an allergen is first exposed to a genetically predisposed individual, it activates Th-2 lymphocytes (contrary to the regulatory T-reg subtype in non-predisposed individuals, which helps in oral tolerance development). These Th-2 cells secrete various cytokines (particularly IL-4 and IL-13) to drive production of allergen-specific IgE immunoglobulin from B cells. The IgE antibodies bind to IgE receptors (FcεRs) on the surfaces of mast cells (as well as basophils). This process is known as sensitization. Upon re-exposure to the same allergen, IgE bound to mast cells and basophils get cross-linked, resulting in the release of preformed and de-novo synthesized inflammatory and vasoactive mediators such as histamine, tryptase, chymase, carboxypeptidase, platelet-activating factor (PAF) and leukotrienes. These induce vasodilation, mucus secretion, smooth muscle contraction, and influx of other inflammatory cells (Figure 2) [15]. This is known as type-1 hypersensitivity reaction and is responsible for IgE-mediated food allergy. Non-IgE-mediated and mixed IgE/non-IgE-mediated food allergies have distinct pathogenesis, and their discussion is beyond the scope of this discussion.

In distinction, food intolerance is non-immune-mediated. Of the multiple causes of food intolerances, the focus is on IBS/FGID and carbohydrate malabsorption. IBS is a common functional gastrointestinal disorder that is characterized by a chronic episodic alteration in bowel habits with associated abdominal discomfort/pain in the absence of an organic cause. The pathophysiology of IBS remains uncertain but it has been suggested that visceral hypersensitivity, gastrointestinal dysmotility, small intestinal bacterial overgrowth (SIBO), altered gut microbiota, psychosocial dysfunction and other factors play a role [16]. Carbohydrate intolerance is another important entity, which can be caused by loss of brush border enzymes (lactose, isomaltose), disorders of transport proteins (fructose-sorbitol malabsorption, glucose-galactose malabsorption) or the inability of gut enzymes to fully metabolize the sugar (e.g., fructan) [17,18]. All conditions lead to increased transport of partially metabolized sugar into the colon, where they are fermented, leading to flatulence and bloating.

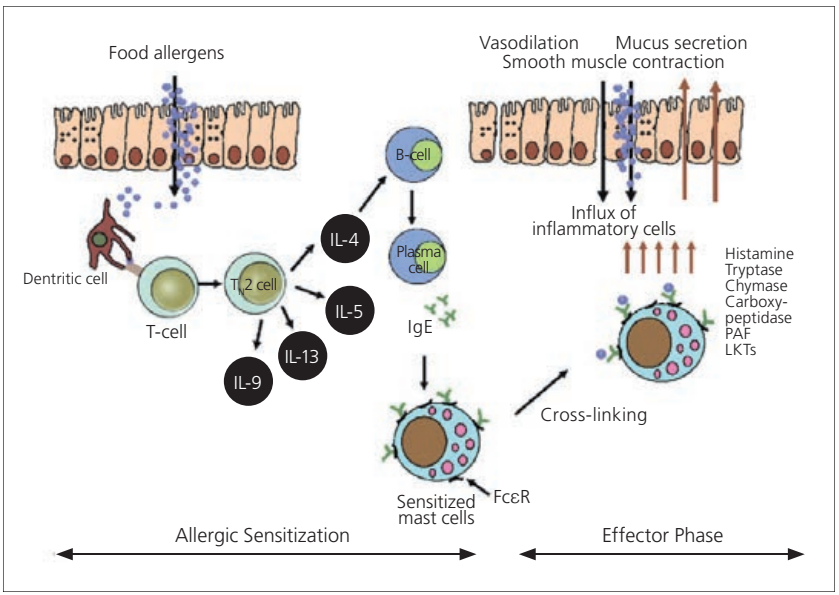


Figure 2: *Classical immune mechanism of IgE-mediated food allergy. Naïve CD4 T cells differentiate into Th2 cells by food proteins and produce type-2 cytokines like IL-4, IL-5, IL-13, and IL9. These type-2 cytokines promote B cells differentiation into IgE-producing plasma cells. Food allergen-specific IgE is distributed systemically and binds to the FceR on mast cells. After sensitization, cross-linking of re-exposed food allergens to allergen-specific IgE that binds to FceR on mast cells induces degranulation of mast cells and release of several kinds of mediators*

Food Allergies and Intolerances: Clinical Presentation

Patients who suffer from adverse food reactions manifest a spectrum of symptoms ranging from transient and benign symptoms such as bloating, hives and loose stools, to potentially life-threatening reactions such as anaphylaxis (associated with IgE-mediated allergy) [19]. Since the patient in our case reported partial improvement of symptoms by avoiding wheat products, we will use adverse reactions to wheat (ARW) as an example to demonstrate the key similarities and differences between food allergy and intolerances. ARW can be seen in such disorders as celiac disease, eosinophilic esophagitis (EoE), IgE-mediated wheat protein allergy and fructan intolerance (which presents as a subset of IBS). Making a diagnosis based on symptoms alone is not always possible as the individual presentations of different ARW can be quite non-specific and may overlap to a great extent.

Food Allergies and Intolerances: Management

Although avoidance of wheat products is the cornerstone treatment for various wheat-related adverse reactions, there are a few subtle but important differences in the management of each of them. A ***four-E*** approach is useful in the management of IgE mediated food allergy [20]. It consists of:

1. ***Elimination of the food trigger:*** this is the key to prevent a food allergic reaction, as there is no cure for food allergy. To eliminate the food trigger, one must be able to correctly identify it
2. ***Early recognition of allergic reaction and anaphylaxis:*** dangerous fatal and near-fatal reactions may occur if the symptoms of the reaction are not recognized quickly and epinephrine administration is delayed [21]
3. ***Epinephrine autoinjector use, when required:*** patients with IgE-mediated food allergy should always carry self-injectable intramuscular epinephrine in case of anaphylaxis due to accidental exposure [22]. Indications to use epinephrine may include mild or severe symptoms from various organ systems. In contrast, patients with non-IgE-mediated food allergic diseases such as celiac disease and EoE do not require self-injectable epinephrine
4. ***Education about food trigger avoidance and cross contamination:*** food trigger avoidance comprises of the elimination of the sources of food harboring the offending allergen. This might appear easy in theory, but its practical application may be challenging. For example, wheat is usually present in pasta, bran, bread crumbs etc., however, hidden sources may include vegetable gum, soy sauce, and flavoring agents. Hence one must check the label of the food product to ensure it is free from the allergen

Patients with IgE-mediated allergy should also be instructed about cross-reactivity with other related foods which the patient has never consumed (as their tolerance is not known), which may lead to restriction of more than just the known allergen. Cross reactivity arises when related foods share the same allergenic protein. For example, fish and tree nuts are commonly cross-reactive, and hence allergy testing (skin prick test and OFC) shall be considered in case tolerance to other nuts or shellfish, respectively, is not known. Grains including wheat, and fruits and vegetables are less likely to be cross reacting [23]. Patients should also be educated about safe storage and cleaning in case there is possibility of cross-contamination with the allergen as non-allergic members of the family continue to consume the food that the patient is allergic to. Additionally, some medications and vaccines usually harbour common allergens, and it is important to inquire about the relevant food allergies before administering them.

In patients with food intolerance and carbohydrate intolerance, treatment might involve avoidance of carbohydrates in addition to fructans, such as lactose and fructose (FODMAPs). In a recent randomized, controlled, single-blind, crossover trial of IBS pa-

tients, Halmos *et al.* [24] found significant reduction of symptoms in more than 50% of patients treated with the low FODMAP diet.

Be Aware of Food Allergy Testing and Treatment

1. One should be aware of the *non-validated* and *unproven* diagnostic tests for food related diseases, as unnecessary dietary restriction can result in malnutrition and disruption of social life
2. It is important to distinguish food intolerance from food allergy because the prognosis, management and nutritional implications are very different
3. Food allergy can be IgE-mediated (IgE-mediated food protein allergy), non-IgE-mediated (celiac disease, eosinophilic esophagitis) or mixed IgE/non-IgE-mediated (atopic dermatitis)

Table 3 summarizes testing for celiac disease and other wheat disorders.

Table 3: Testing for celiac disease and other wheat disorders (from Boyce *et al.* [22])

Test type and substrate	Companies in the USA	NIH Expert Panel Recommendations
IgE in serum	Many commercial food specific IgE	Food allergy (FA)
IgA in serum, saliva	Some commercial food specific IgA	Not recommended
IgG in serum, saliva	Some commercial food specific IgG	Not recommended
IgG4 in serum, saliva	Some commercial food specific IgG4	Not recommended
Skin prick with food extracts	Food extracts/fresh food extracts	Food allergy
Leukocyte cytoxicity assays	ALCAT	Not recommended
tTG IgA, IgG, serum	Many companies	Celiac disease (CD)
DGP IgA, IgG, serum	Many companies	Celiac disease
Native gliadin IgG	Lab Corp	Not recommended
Intestinal antigen permeability	Cyrex, others	Not recommended
Celiac serology, HLA in stool	Enterolab	Not recommended
Applied kinesiology		Not recommended
Electrodermal skin testing		Not recommended
MRT/LEAP – measures release of immune mediators (histamine, cytokines) via change of liquid/ solids ratio in a blood sample		Not recommended
* = Expert NIH panel "recommends not using" this test for routine diagnosis of food allergy		

In summary, adverse reactions to food can entail many different dietary products, modifiers and mechanisms of action. A thorough understanding of the different categories assists in the development of an effective approach for diagnostic work up, treatment and prevention. The common elements for the patient begin with an accurate assessment, education, avoidance of the offending food and in the cases of allergy, awareness of the need for urgent management of anaphylaxis.

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Ángel Lanas

16:00 NSAID-enteropathy: Diagnosis, Prevention and Treatment

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Introduction

Non-steroidal antiinflammatory drugs (NSAIDs) are one of the most frequently used medications worldwide, due to their efficacy as analgesic and antiinflammatory agents. However, it is well known that their use may be associated with a broad spectrum of adverse events. Those originated in the gastrointestinal (GI) tract are the most common. Today, it is widely accepted that NSAIDs can damage the entire GI tract (i.e. the esophagus, stomach, duodenum, jejunum, ileum and colon) [1].

NSAIDs are frequently co-prescribed with proton pump inhibitors (PPIs) in patients with increased GI risk to prevent NSAID-associated gastro-duodenal damage and symptoms [2]. However, while PPIs reduce the development of peptic ulcer and related complications in patients taking NSAIDs, their beneficial effect does not take place beyond the duodenum. NSAID-gastropathy is indeed a pH-dependent phenomenon and the mucosal protection induced by PPIs is mainly ascribed to their antisecretory effect [2].

The availability of video capsule endoscopy (VCE) and enteroscopy has allowed visualization of mucosal lesions of the small bowel and related complications, associated with NSAIDs use [3]. The magnitude of the damage in the small bowel may exceed that seen in the upper GI tract, although the clinical relevance of the lesions detected with these techniques still await further longitudinal studies [4,5]. However, large coxib clinical trials and observational studies have pointed out that NSAIDs use is associated with increased risk of complications of the lower GI tract (small bowel beyond the angle of Treitz and the colon) [6]. In fact, over the past decades, there is a progressive change in the overall pattern of GI events leading to hospitalization, with an evident decreasing trend in upper GI events and an increase in lower GI events [7].

Mechanisms of NSAID-induced Intestinal Mucosal Damage

NSAID-induced damage to the GI tract is the consequence of two main mechanisms, which involve mucosal COX-inhibition and the topical effect of NSAIDs together with luminal factors. COX-1 is one of the two well-defined COX isoenzymes, which is present in most tissues. COX-1 has been associated with hemostasis regulation,

GI tract integrity, platelet function, and macrophage differentiation. It is involved in the synthesis of endogenous prostaglandins that stimulate the production and secretion of mucus and bicarbonate, increase mucosal blood flow, and promote epithelial cell proliferation. In contrast, COX-2 is an inducible enzyme, expressed in inflammatory conditions, and is the primary target of NSAIDs. NSAID inhibition of COX enzymes has important implications in the mucosal microcirculation and induces the expression of neutrophil adhesion molecules within the endothelium that could mechanically compromise microvascular blood flow. Several studies in animals have shown that the absence or selective inhibition of COX-1 reduced the level of prostaglandins by 95% or more, without increasing intestinal permeability, inflammation, or ulcers [8]. Similar effects were observed with short-term selective deletion or inhibition of COX-2, suggesting that both isoenzymes should be inhibited to disrupt GI mucosal integrity [9].

The other mechanisms involved in the pathogenesis of NSAID-induced damage to the GI tract are COX-independent. Traditional NSAIDs are lipid-soluble, weak acids. Topical effects involve detergent-like interactions with phospholipids and the uncoupling of cellular oxidative phosphorylation [10]. NSAIDs interact with the mucus layer and the phospholipid bilayer of the GI tract. They decrease the hydrophobicity of GI mucosal lining, which leads to mucosal exposure to different luminal aggressors, such as acid and pepsin in the stomach and bile in the small bowel. On the other hand, NSAIDs uncouple mitochondrial oxidative phosphorylation, even at millimolar concentrations [10], leading to a cascade of detrimental effects that causes cellular ATP depletion and loss of intercellular junction integrity in the GI tract. These effects increase mucosal permeability, apoptosis and cell death. COX-2-selective agents can also uncouple oxidative phosphorylation, but with lower potency compared to traditional (i.e. non-selective) NSAIDs [11]. Topical effects can initiate GI damage, but the addition of COX-1 inhibition and luminal aggressors causes increased intestinal permeability, low-grade inflammation, mucosal erosions and ulcers.

Inhibition of COX-derived mucosal prostaglandin synthesis occurs along the entire GI tract, but there are marked differences between the gastroduodenal mucosa and the small or large bowel in the concurrence of luminal factors. This aspect seems to play a substantial role in NSAID-induced mucosal damage. The absence of acid and the presence of bacteria and bile are the most relevant differences between the stomach and the small bowel and colon, which will substantiate our options for treatment and prevention [12]. Some studies have suggested that the combination of bile and NSAIDs is more toxic than either agent alone. The severity of NSAID-enteropathy correlates to the amount of the drug excreted in bile and the extent of enterohepatic circulation (Figure 1) [10]. Experimentally, the absence of bile in the gut (bile duct ligation) almost completely abolishes the small intestinal damage induced by NSAIDs [10]. On the other hand, bile triggers biotransformation of some NSAIDs, leading to conjugates that can be harmful. Commensal bacteria play a role in the metabolism

of these NSAID conjugates, by deconjugating them into even more toxic compounds [13], which explain mild and distal location of NSAID enteropathy.

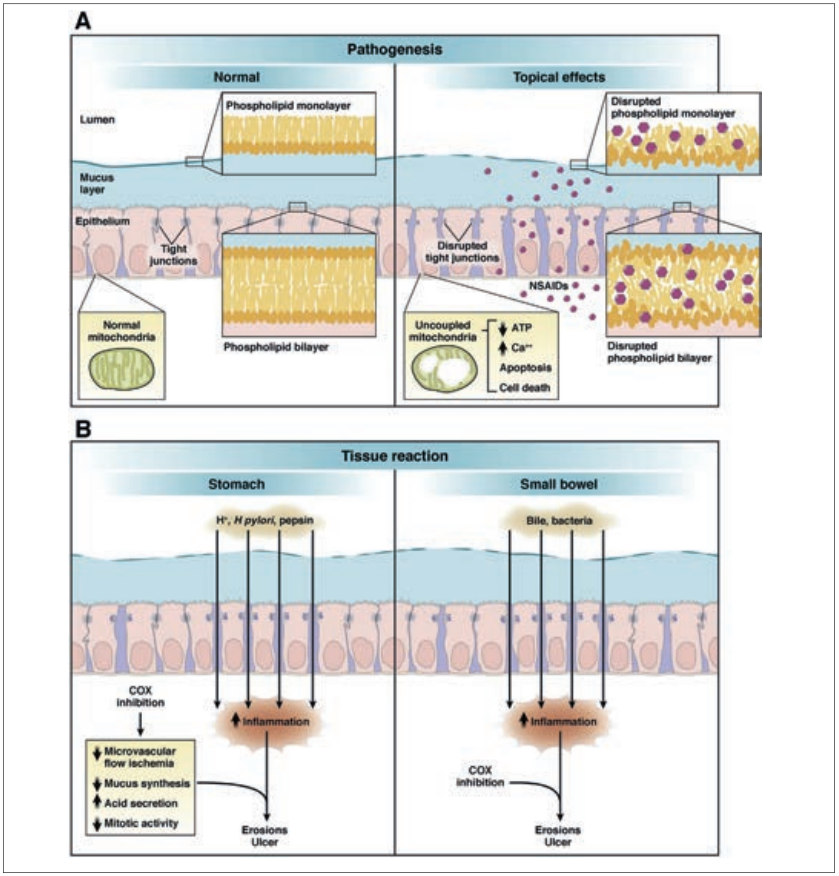

Figure 1: *Mechanisms of gastrointestinal damage by NSAIDs. In this model, the interaction between NSAIDs and phospholipids and uncoupling of oxidative phosphorylation damage intestinal cells and increase gastrointestinal permeability. Inhibition of COX reduces microvascular blood flow, and luminal aggressive factors modify and amplify this reaction, leading to inflammation, erosions, and ulcers. Principal luminal aggressors are acid and pepsin in the stomach and acid, bile, and bacteria in the small bowel. (from Bjarnason* et al. *[10])*

Currently, the interaction of gut microbiota and consequent activation of the innate inflammatory cascade is considered to play a key role in the pathogenesis of NSAID-induced mucosal damage in the small intestine [10,14]. NSAID-induced mucosal permeability facilitates the action of bacteria, and the lipopolysaccharide components present in gram-negative intestinal bacteria can activate the transmembrane toll-like receptor (TLR-4) present in intestinal cells. TLR-4 promotes mucosal cytokine expression, which leads to neutrophil recruitment, and finally, the release of reactive oxygen species and proteases that cause mucosal injury [15]. Early studies already reported that metronidazole [16] was able to reduce inflammation and blood loss in patients taking NSAIDs, suggesting that antimicrobials could have therapeutic potential in this setting. A recent proof-of concept study showed that diclofenac-induced small bowel lesions were reduced by the co-administration of the poorly absorbable antibiotic, rifaximin [14].

Type of Lesions

NSAIDs cause a wide spectrum of lesions in the lower GI tract. Increased gut permeability and inflammation has been reported to be present in up to 70% of patients taken NSAIDs long-term, but it is often silent and is not observed with NSAIDs that do not undergo entero-hepatic circulation [10,17]. Discontinuing long-term NSAID treatment is not followed by a rapid return to mucosal normality, since abnormalities can be detected up to 3 years later. Other clinical manifestations include blood loss and anemia, malabsorption, protein loss, and mucosal ulceration [18]. Ulcers may complicate with bleeding, and more rarely with perforation or strictures. Typical NSAID-induced strictures in the small bowel are often multiple and adopt the form of annular stenosis, nicely described by Bjarnasson's team in the late eighties [19].

Long-term NSAID treatment can induce enteropathy associated with mild blood loss, which might result in anemia or iron deficiency. A systematic review of randomized trials, which included 1162 subjects found that most individuals taking NSAIDs or aspirin, exhibited an average increase in fecal blood loss of 1-2 ml/day, (0.5 ml/day baseline with no treatment). Some individuals may lose much more blood than average; 5% of individuals taking NSAIDs had blood losses of 5 ml/day or more, and 1% of individuals can actually loose 10 ml/day or more [20].

Mucosal ulcerations or mucosal breaks (mucosal denudation, erosions, ulcers), as it is often seen in the two-dimensional vision of VCE, are very common in NSAID users. One study [21] reported that both long-term non-selective and COX-2 selective NSAID treatment were associated with this type of lesions (reddened folds, mucosal denuded areas and mucosal breaks) in 62% and 50% of patients, respectively. In the colon, NSAIDs use has been associated with inflammation, erosions, or superficial solitary or multiple ulcers, lymphocytic colitis and collagenous colitis [22].

Although the clinical relevance of these lesions are not fully understood, they may explain the reported increased rate of hospitalizations due to lower GI bleeding. The MEDAL study program evaluated the occurrence of severe upper and lower GI events in 34.701 patients with rheumatoid arthritis or osteoarthritis with a mean therapy duration of 18 months [23]. Lower GI complication rates (including perforation, obstruction, or bleeding) were 0.32 and 0.38 per 100 patient-years, for etoricoxib and diclofenac respectively. Bleeding was the most frequent complication (0.19 and 0.23 per 100 patient-years, for etoricoxib and diclofenac, respectively). Another study [24] concluded that nonselective or selective NSAID use was associated with lower GI bleeding (OR: 2.3, 95% CI: 1.6-3.2). In addition, a recent case-control study found an association of NSAID use with increased risks of both upper (RR: 2.6, 95% CI: 2.0-3.5) and lower GI bleeding (RR: 1.4, 95% CI: 1.0-1.9) [1]. Other studies confirmed this findings with aspirin [25]. Complicated colonic diverticular disease is another adverse effect associated with NSAIDs and aspirin in the lower GI tract. A systematic review and meta-analysis of observational studies concluded that both aspirin and NSAID use were strongly associated with an increased risk of colonic diverticular bleeding (RR: 2.48, 95% CI: 1.86-3.31) [26].

Diagnosis

The most frequent clinical test used in the diagnosis of NSAID-induced enteropathy is *VCE*, but it is not the only option (Table 1). Different biochemical test can also be used to detect the presence of inflammation and abnormal intestinal permeability.

Table 1: Methodology to assess NSAID-enteropathy and associated pathophysiology changes

Methodology	Comment
Video capsule endoscopy	Usually is the first diagnostic tool to be used
Enteroscopy with single or double balloon	Used to confirm or treat lesions found with VCE. Needs deep sedation and considered invasive
Magnetic resonance	Widely used in patients with IBD. Useful to detect strictures and gross morphological changes
CT scan, Barium meal	Low use if magnetic resonance is available
Lactulose/Mannitol test	Urinary biochemical test to detect increase in gut permeability
Calprotectin	Determined in feces. Detects the presence of inflammation

VCE examines the morphology of the entire small bowel mucosa with minor discomfort to patients (Figure 2) [27]. Images and descriptive data of the location of lesions are recorded as thumbnail photographs. NSAID-induced lesions are categorized based on different classifications. One of the most widely used is that reported by Graham *et al.*, [28] who assumed that erosions and ulcers cannot be reliably distinguished in capsule images. Lesions were classified as category 0, when no lesions are found; category 1 for the presence of petechiae/red spots; category 2, when a small number of erosions (n = 1–4) were detected; category 3 with higher number of erosions (n > 4); and category 4, for the presence of large erosions or ulcers. Other classifications, based on similar findings, are available and some differentiate lesions in the proximal (jejunum) or distal (ileum) small bowel.

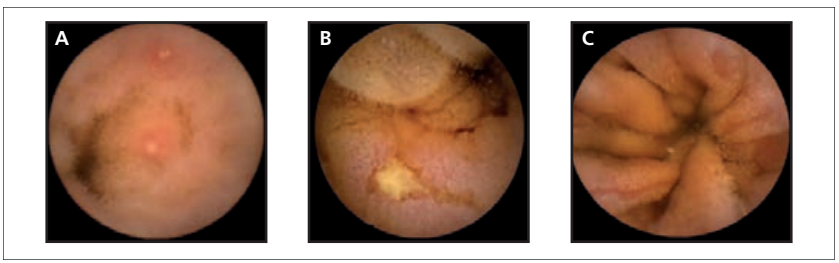

Figure 2: *Video capsule endoscopy. Images of the small-bowel injury induced by NSAIDs:* **A**) *erosions;* **B**) *ulcer;* **C**) *denuded areas. (from Fujimori* et al. *[27])*

Single or double balloon *enteroscopy* can also be used for the diagnosis of NSAID-induced enteropathy, but in general this technique is performed after VCE with the aim of confirming and/or treating lesions already seen or suspected by the non-invasive technique (Figure 3) [29]. Finally, barium meal, magnetic resonance imaging of the small bowel, CT scans, etc. can be used to determine the presence of suspected strictures before performing a VCE test or in presence of GI complications.

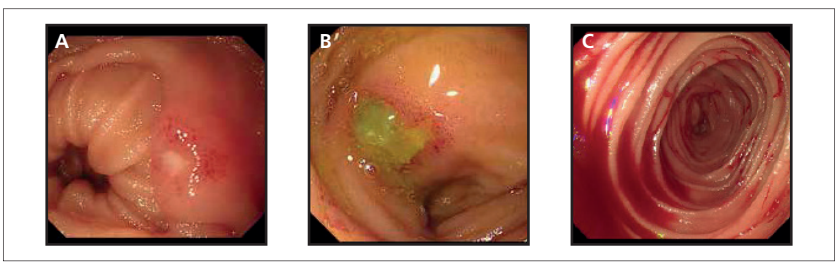

Figure 3: *Single balloon endoscopy. Images of the small-bowel injury induced by NSAIDs:* **A**) *erosion;* **B**) *round ulcer;* **C**) *active bleeding. (from Xu* et al. *[29])*

Noninvasive Tests of Intestinal Damage

Permeability of the intestine can be determined upon the ingestion of sugar probes (sucrose, lactulose, and mannitol). Sucrose measures gastroduodenal permeability and does not detect small intestinal damage, since it is rapidly degraded, making it specific for the upper gastrointestinal tract [30]. The ratio of lactulose to mannitol excretion in urine however has been used to determine the presence and extent of increased intestinal permeability [31].

Finally, the concentration of fecal calprotectin can be measured by enzyme-linked immunoassay and correlates with the presence of gut inflammation. This test, originally developed for the follow-up of IBD patients, can also be used to detect NSAID-induced enteropathy. It has been shown that even short-term NSAID treatment may increase calprotectin concentrations in some patients [30]. The correlation of these tests with the presence/absence of visible lesions by VCE in the small bowel is however not clearly established [31].

Treatment of NSAID-enteropathy

Unlike the upper GI tract, where there is evidence that antisecretory drug treatment with PPIs, high dose famotidine or misoprostol can heal peptic ulcers and erosions associated with NSAID use, the best therapy to heal NSAID-related mucosal breaks in the small bowel needs still to be defined (Table 2).

Misoprostol is probably one of the best options to heal NSAID-induced mucosal breaks in the small bowel. In a small double-blind, randomized, placebo-controlled trial [32] misoprostol (200 µg, 4 times daily) was studied for its healing effect of small bowel ulcers, associated with small bowel bleeding in patients requiring continuous aspirin therapy. Complete healing of small bowel ulcers was observed in 28.6% of patients (95% CI, 14.9%-42.2%) taking misoprostol vs 9.5% (95% CI 0.6%-18.4%) in the placebo group (p =.026). The misoprostol group had also a significantly greater mean increase in hemoglobin levels than the placebo group (mean difference, 0.70 mg/dL; 95% CI, 0.05-1.36; p =.035). In another recent, randomized, double-blind, placebo-controlled study [33], the efficacy and safety of misoprostol for the treatment of small bowel ulcers and erosions in patients taking low-dose aspirin or NSAIDs with obscure gastrointestinal bleeding was assessed. Patients with small bowel ulcers, taking low-dose aspirin, NSAIDs or both for a minimum of 4 weeks, and evidence of obscure gastrointestinal bleeding and normal upper and lower endoscopy, were randomly assigned to receive 200 µg oral misoprostol or placebo four times daily for 8 weeks. The primary endpoint was the complete healing of small bowel ulcers and erosions. Complete healing of small bowel ulcers and erosions at week 8 was 54% in the misoprostol group and 17% in the placebo group (p =0.0002). No differences in adverse events between groups were reported.

Table 2: Therapeutic approaches in the prevention or treatment of small bowel lesions induced by NSAIDs or aspirin

Therapy	Potential indication	Comment
COX-2 selective agents (celecoxib)	Prevention	Less damaging agent than non-selective NSAIDs
Misoprostol	Healing and Prevention	Consistent results for both indications. High doses needed and potential adverse events
Rebamipide	Healing and Prevention	Less evidence compared to misoprostol. Only used in Asia. More studies needed
Metronidazole	Healing and Prevention	Experimental evidence. More studies in humans needed. Concerns with antibiotic resistance
Rifaximin	Healing and Prevention	Proof-of concept study positive. Non-absorbable; safety profile compared to other antibiotics. Studies in patients needed
Probiotics	Healing and Prevention	Best probiotic or mixture of probiotics not defined Attractive approach but evidence is limited, and more studies are needed
Other options (inhibitors of bacterial β-glucuronidase, teprenome, lansoprazole, lactoferrin, soluble dietary fiber, H2S-NSAIDs, phosphatidylcholine-NSAIDs)	Healing and Prevention	Only experimental data available. Current evidence very limited

Rebamipide, an amino acid analog of 2-(1H)-quinolinone used in Asian countries as a mucosal protecting compound for gastric ulcers, has also been tested in the small bowel. It induces a decrease in the generation of oxygen radicals, increases mucosal blood flow and induces prostaglandin secretion of the mucosa, which accelerates

the process of healing. A multicenter, randomized, double-blind, placebo-controlled trial [34] assessed the efficacy of high-dose rebamipide in patients with low-dose aspirin-induced moderate-to-severe enteropathy. Patients on daily aspirin (100 mg of enteric-coated) should have had more than 3 mucosal breaks (i.e., erosions or ulcers) in the small intestine, as assessed by VCE. Eligible patients received either rebamipide 300 mg 3 times daily or placebo for 8 weeks. Capsule endoscopy was then repeated. Rebamipide, but not placebo, significantly decreased the number of mucosal breaks ($p = 0.046$). The rate of complete mucosal break healing in the rebamipide group (32%) tended to be higher than the 7.7% observed in the placebo group. A systematic review also confirmed the effects of rebamipide although the authors concluded that better designed studies were needed [35]. The rebamipide-misoprostol combination has been reported to improve anemia in a patient with small bowel ulcers [36].

The use of ***antibiotics*** to reduce or modify the intestinal microbiote may be another approach. In patients with established NSAID enteropathy, metronidazole reduced inflammation and bleeding but did not affect intestinal permeability [37]. New studies should be performed in patients with poorly absorbable antibiotics such as rifaximin (*see prevention section*).

Prevention

Prevention of small bowel (or colonic) lesions and complications in patients taking NSAIDs, must be considered in the frame of a wider approach of preventing NSAID-induced lesions in the whole GI tract (Table 2). This means that patients will be taken or prescribed PPI as part of the prevention strategy for the upper GI tract. PPIs or any other antisecretory drug will not prevent damage to the lower GI tract and therefore other (or additional) options must be considered. In addition, it is worthwhile to emphasize that some studies have shown that PPIs may actually increase the incidence of NSAID-associated small bowel injury by inducing dysbiosis [*for review see* 38]. A small randomized, double-blind, controlled study of 57 healthy subjects [39] given either celecoxib (200 mg, twice daily) plus placebo for 2 weeks or celecoxib plus the PPI rabeprazole (20 mg, once daily) for 2 weeks showed a significantly higher proportion of subjects in the celecoxib + PPI group with small bowel injury (44.4%) compared to celecoxib+placebo group (16.7%; $p = .04$). The number of erosions in each member of the celecoxib+PPI group was greater than in each member of the COX-2 + placebo group ($p = .02$). However, the number of ulcers did not differ between groups. The clinical relevance of this findings needs to be defined.

One alternative to the combination of NSAID and PPI and to reduce NSAID-induced damage to the *entire* GI tract may be the prescription of selective COX-2 inibitor, celecoxib. The CONDOR trial was a multi-center, double-blind study [40] that randomly assigned 4484 patients to receive celecoxib alone or diclofenac slow-release plus PPI, and evaluated the risk of GI events in each group. The risk of clinically significant

upper and lower GI events (anemia included) was higher with diclofenac plus PPI than with celecoxib (HR: 4.3, 95% CI: 2.6–7.0; p<0.0001). Other studies have also confirmed that celecoxib is GI safer alternative to NSAID-PPI combination both in the upper and lower GI tract, with the advantage of reducing the established NSAID-associated intestinal lesions after switching to this selective COX-2 agent [41].

However, to avoid or minimize NSAID-induced damage to the lower GI tract, new strategies, other than COX-2 selective agents, are needed. *Misoprostol* may not only heal but prevent the development of lesions induced by NSAID or selective COX-2 inhibitors. A single-blind, randomized, controlled trial [42] in 34 healthy male volunteers, receiving diclofenac plus omeprazole (25 mg 3 times daily and 20 mg once daily, respectively) treatment, showed that addition of misoprostol, (200 µg 3 times daily), prevented NSAID-induced mucosal breaks (p =0.42). Other gastric protectants such as *rebamipide* may not only treat but also prevent small bowel mucosal lesions induced by NSAIDs, although further studies are needed [43].

Interference with luminal aggressors is an interesting approach. Bile and bacteria play relevant roles in the NSAID-induced enteropathy [10]. Bacterial β-glucuronidase in bile can deconjugate NSAIDs, and metabolites can be toxic to GI mucosa. Some animal studies have shown that specific inhibitors of bacterial β-glucuronidase [10] could reduce small bowel lesions induced by NSAIDs. These compounds have not been tested in human clinical trials, as yet.

Increasing evidence from animal studies suggests that intestinal bacteria contribute to NSAID-enteropathy. Enterobacteria represent therefore an attractive target in humans both for prevention and treatment. A proof-of concept study [14] has recently evaluated the efficacy and safety of a delayed-release formulation of *rifaximin* [Rifaximin-Extended Intestinal Release (EIR)], a broad spectrum and poorly absorbed antibiotic, in the prevention of diclofenac-associated lesions evaluated by VCE. Sixty subjects were randomized to rifaximin or placebo. The number of subjects developing at least a mucosal break was 20% in the rifaximin group and 43% in the placebo group, while the change in the mean number of mucosal lesions was 0.3±0.7 and 1.2±2.3, respectively. Finally, 9 placebo-treated subjects developed large erosions or/and ulcers at the end of treatment, but no rifaximin-treated volunteer presented such severe lesions. These findings demonstrate an overall protective effect of rifaximin on diclofenac-associated mucosal lesions in healthy volunteers.

Another alternative approach is to reduce or prevent NSAID-induced small bowel damage with probiotics. However, the results from studies of probiotics have been inconsistent, so far. In a clinical trial, the probiotic VSL-3 prevented the small bowel damage due to indomethacin (50 mg/day), assessed by fecal levels of calprotectin [44].

In patients taking aspirin and a proton pump inhibitor who had iron-deficiency anemia, the probiotic *Lactobacillus casei* (DN-114 001) significantly reduced mucosal damage determined by VCE, compared with controls [45]. In another study, the use of yogurt containing *Lactobacillus gasseri* seemed to mitigate aspirin-induced small bowel injuries [46]. However, additional studies need to be performed before probiotics can be recommended for prevention or treatment of NSAID-enteropathy in humans.

Finally, in addition to those options mentioned above, *other treatments* have been tested, mainly within different experimental settings, and therefore still far from being considered within our therapeutic armamentarium. These therapies include GI-sparing NSAIDs (NO- or H2S-NSAIDs, NSAIDs mixed with phosphatidylcholine), other anti-ulcer drugs such as teprenone, anti-secretory agents such as lansoprazole, different types and mixtures of probiotics and food constituents (lactoferrin and soluble dietary fibers) [47].

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Giovanni Barbara

17:00 Pathophysiology and Therapy of Functional Bowel Disorders
Focus on Irritable Bowel Syndrome

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Functional bowel disorders (FBD) encompass a spectrum of chronic gastrointestinal (GI) disorders characterized by predominant symptoms or signs of abdominal pain, bloating, distention, and/or bowel habit abnormalities (e.g., constipation, diarrhea, or mixed constipation and diarrhea). The FBDs are classified into 5 distinct categories: irritable bowel syndrome (IBS), functional constipation (FC), functional diarrhea (FDr), functional abdominal bloating/distention, and unspecified FBD (Table 1) [1].

Table 1: Functional bowel disorders

1. Irritable bowel syndrome
2. Functional constipation
3. Functional diarrhea
4. Functional abdominal bloating/distension
5. Unspecified functional bowel disorders
6. Opioid-induced constipation

IBS is the most common entity amongst FBDs. It is characterized by recurrent abdominal pain, associated with defecation or a change in bowel habits. Disordered bowel habits are typically present (i.e., constipation, diarrhea, or a mix of constipation and diarrhea), as are symptoms of abdominal bloating/distention. Symptom onset should occur at least 6 months before diagnosis and symptoms should be present during the last 3 months. IBS is the most common FGID affecting up to 15% of the Western population, it is associated with reduced quality of life and high social costs. IBS etiology is poorly defined and considered to be multifactorial. IBS represents a challenge for the general practitioner and gastroenterologist alike [1].

Pathophysiology

Although the pathophysiology of IBS is not completely understood the condition has been attributed to a dysregulation of the brain-gut axis, involving [2-3]:

- psychosocial factors
- changes in intestinal motility
- visceral hypersensitivity.

Recently, molecular, biochemical and genetic abnormalities have been identified, including: genetic factors and polymorphisms, altered enteroendocrine metabolism (e.g., serotonin), neuroplastic changes, gastrointestinal infections, altered microbiota, dietary factors, mucosal and systemic immune activation, and increased mucosal permeability (Figure 1) [4].

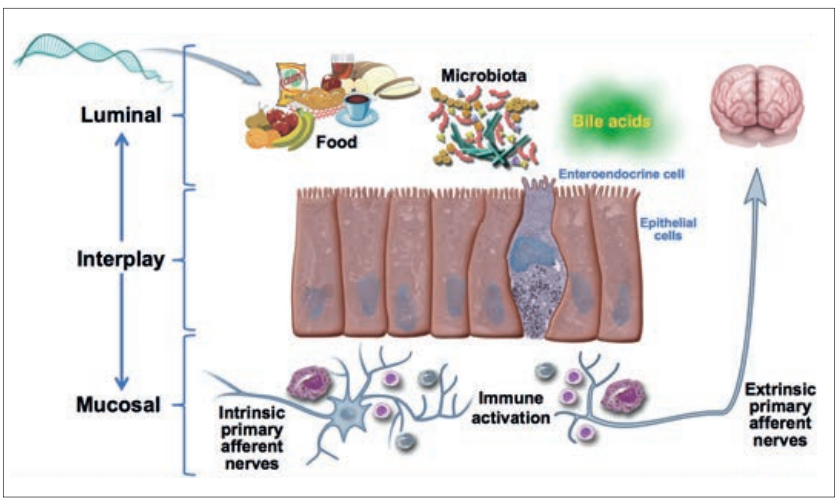

Figure 1: *Schematic representation of the putative interplay between luminal and mucosal factors in FGIDs. Microenvironmental factors (e.g., food, microbiota, bile acids) may permeate in excess through a leaky epithelial barrier, allowing amplification of signaling from the lumen to deeper mucosal and muscle layers, including overstimulation of the mucosal immune system. These factors may determine abnormal signaling to neural circuits (intrinsic primary afferent nerves and extrinsic primary afferent nerves), which in turn may affect intestinal physiology and sensory perception*

Brain-gut axis dysregulation. Brain dysfunction and abnormal interaction of the peripheral and central nervous system are potential mechanisms involved in symptom

generation in IBS. The importance of a bi-directional interaction between central and peripheral mechanisms is supported by several lines of evidence and have been reviewed elsewhere [2]. Interestingly, in a longitudinal study, in people free of FGIDs at baseline, anxiety was significantly associated with new onset FGIDs 12 years later. In people, free of psychological factors at baseline, FGIDs was significantly associated with anxiety and depression at follow-up, suggesting that IBS is not "all in the head" in all patients [5].

Genetic factors. Overall, IBS displays features of a complex disorder with interactions between environmental and genetic factors. Several studies evaluated the risk effects of single nucleotide polymorphisms (SNPs) in IBS candidate genes. Post infectious IBS was associated with SNPs in genes involved in immune activation, epithelial barrier and host-microbiota interaction (TLR9, IL-6, and CDH1). A recent study demonstrated in two independent cohorts from Sweden and USA a strong association between rs4263839 in *TNFSF15* and IBS, particularly IBS-C. The first genome-wide association study (GWAS) in IBS identified a suggestive locus at 7p22.1 with genetic risk replicated in all case-control cohorts. The genes *KDLER2* and *GRIP2IP* map to the associated locus. Interestingly, *KDLER2* gene products were involved in host-microbiota interactions [6]. More recently, a GWAS meta-analysis encompassing 5 population-based cohorts including 1335 IBS cases and 9768 controls showed the implication of ion channel genes in the pathogenesis of IBS [7].

Enteroendocrine metabolism alteration. Serotonin, or 5-hydroxytryptamine (5-HT), released by a subtype of enteroendocrine cells named enterochromaffin cells in response to mechanical and chemical stimuli regulates gastrointestinal secretory, motor, and sensory functions throughout receptors spread all over the gut. Decreased postprandial 5-HT platelet-depleted plasma levels have been reported in IBS-C, while increased plasma levels of 5-HT have been shown under fasting and fed conditions in IBS-D or PI-IBS. Colonic expression of serotonin reuptake transporter (SERT), the main catabolic pathways of 5-HT activity, was demonstrated to be reduced in patients with IBS, although conflicting data have been reported. Other data showed an increased spontaneous release of 5-HT in patients with IBS irrespective of bowel habit that correlated with the severity of abdominal pain [4].

Neuroplastic changes. Several studies described neuroplastic changes in patients with IBS. A pioneering study showed that the overall density of mucosal innervation, substance P and transient receptor potential vanilloid type-1 was increased in patients with IBS. A recent innovative study demonstrated an increased density of mucosal nerve fibers and nerve outgrowth as well as neuronal growth factor (NGF) expression in patients with IBS. Mediators from IBS biopsies evoked neurite elongation and neuronal differentiation in culture neuronal cell lines. NGF of immune cell, particularly mast cell origin, was the main mediator involved in these changes. All together, these data suggest that an abnormal mucosal milieu play a role in the pathophysiology of IBS inducing long-lasting neuroplastic changes [4].

Gastrointestinal infections. Acute infectious gastroenteritis is the strongest known risk factor for the development of IBS (the so-called post-infection IBS), with an increase by a factor of six in the odds ratio for IBS. PI-IBS develops in about 10% of patients with infectious enteritis. Post-infection IBS may develop after bacterial infection (e.g. Shigella, Salmonella, and Campylobacter), viral or parasitic gastroenteritis. Risk factors for PI-IBS include the virulence of the pathogen, younger age, female sex, the long duration of the initial gastroenteritis, the use of antibiotics, and psychological factors. A long-term (16-years), prospective, controlled, culture-proven, follow-up study examining the association between a single episode of *Salmonella* gastroenteritis and new-onset FGIDs showed that Salmonella-induced gastroenteritis during childhood, but not adulthood, is a risk factor for IBS. The Rome Foundation has produced a working team report which summarized the available evidence on the pathophysiology of PI-IBS and provided guidance for diagnosis and treatment, based upon findings reported in the literature and clinical experience (Figure 2) [8].

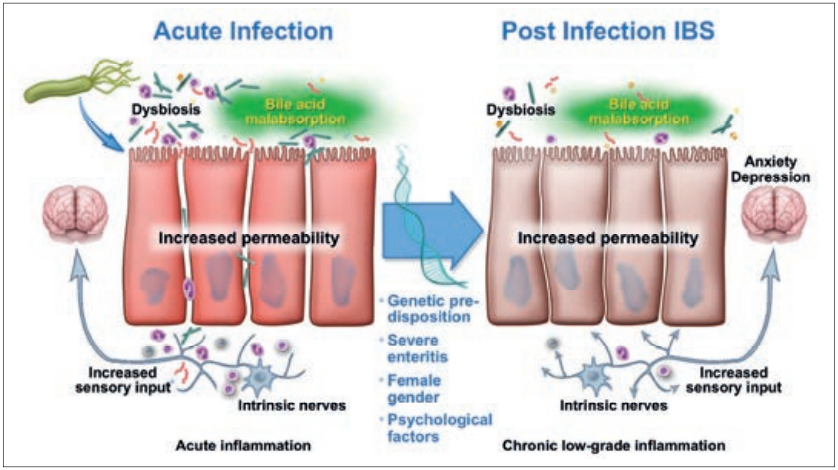

Figure 2: *Schematic representation of putative pathophysiology underlying post-infection irritable bowel syndrome. Acute infection with bacteria, viruses or parasite pathogens generates intestinal dysbiosis, bile acid malabsorption, increased intestinal permeability of luminal factors, participating in mucosal acute inflammation. Inflammatory cells release factors that provide abnormal signaling to neural circuits including intrinsic nerves and sensory nerves conveying increased input to the central nervous system. Following recovery from the acute infection, in genetically predisposed subjects, particularly after severe enteritis and more likely in female subjects, abnormal gut physiology may persist. This includes dysbiosis, bile acid malabsorption, increased permeability, low grade mucosal inflammation and abnormal neuro-immune interactions, involved possibly in the pathogenesis also of anxiety and depression via excessive sensory input to the central nervous system*

Altered intestinal microbiota. The introduction of molecular techniques using high throughput DNA technologies to investigate gut microbiota has renewed interest in intestinal microbiology. Recent studies indicate a different composition of fecal and intestinal mucosal microbiota in patients with IBS. The most consistent abnormality identified in these subjects includes an increased Firmicutes/Bacteroides ratio in all or at least a subgroup of patients with IBS, with decreased levels of Bifidobacteria and members of the genus *Faecalibacterium* (which includes *F. prausnitzii*). Interestingly, patients with abnormal Firmicutes/Bacteroidetes ratio showed changes in bowel physiology including altered bowel transit times, while those with normal microbiota had more psychological impairment (i.e. anxiety and depression).

A correlation between microbial dysbiosis and expression of several host gene pathways, including cell junction integrity and inflammatory response, was demonstrated in PI-IBS and IBS-D. The role of microbiota in FGIDs including IBS has been the subject of exhaustive recent reviews [4,9].

Dietary factors and bile acid malabsorption. Food ingestion frequently exacerbates symptoms in patients with IBS. Attention has been recently directed on gluten and fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs). A randomized controlled trial of a gluten-containing diet versus a gluten-free diet in IBS-D showed that subjects receiving gluten presented a worsening of digestive symptoms associated with increased permeability *(see below)*. FODMAPs are poorly absorbed in the small intestine and reach the colon where they are fermented by bacteria with consequent abnormal production of gas. Diets containing low-FODMAPs have been shown to be beneficial in IBS, although their applicability in everyday practice remains unclear. An increased bile acid synthesis or excretion has been identified in about one-third of patients with IBS-D. Excessive colonic bile acids stimulate secretion and motility as well as pain pathways. A recent trial with colesevelam, a bile acid sequestrant, showed promising results in IBS-D [4].

Increased mucosal permeability. Several structures contribute to the intestinal mucosal barrier, including microbiota, mucus layer, enterocytes, and intercellular tight junctions (TJs), adherent junctions and desmosomes positioned between epithelial cells. All together these components regulate the intestinal permeability. Disruption of the mucosal barrier leads to contact between environmental antigens and mucosal immune system, with subsequent immune activation, stimulation of sensory pain pathways, and, finally, pain perception. Increased mucosal permeability has been first shown in patients with PI-IBS, and subsequently confirmed in patients not only with IBS-D, but also with IBS-C and IBS-M. An increased permeability has been demonstrated by means of *in vivo* (including confocal laser endomicroscopy) and *in vitro* methods both in the small intestine and in the colon, and it was correlated with the main symptom of IBS, the abdominal pain. In addition, this abnormality was fre-

quently associated with a lower expression of mucosal zonula occludens mRNA (one of the main TJ components). The trigger factors involved in the increased intestinal permeability of IBS remain elusive, although recent studies suggest the participation of genetic factors, stress, food antigens, gluten, or luminal factors [4].

Immune activation. The potential involvement of immune activation in the pathogenesis of IBS is suggested by the development of IBS after a bout of gastroenteritis and the increased prevalence of IBS-like symptoms in patients with microscopic colitis, inflammatory bowel diseases in remission, or celiac disease on a gluten free diet. Although mixed results are reported, an increased number of mast cells in the gut of patients with both IBS-D and IBS-C are the most consistent outcome across all the studies assessing immune activation in IBS. In addition, several studies described an increase amount of other immune cells including T cells along with increased release of immune mediators (e.g. cytokines, prostanoids, histamine, tryptase, and proteases) in the intestinal tissue and systemic circulation. The abnormal release of these bioactive factors in the intestinal milieu may impact on gut nerve intrinsic and/or extrinsic activity, as demonstrated by their adoptively transfer to naïve animals or human tissues which increased intestinal submucous neuron excitability, mesenteric sensory nerve activity, and visceral sensitivity. Furthermore, mast cells activated near colonic nerves correlated with the severity and frequency of abdominal pain. All together these studies provide not only evidence of immune infiltration and activation in subgroups of patients with IBS, but also implications of these dysfunctions in the alteration of intestinal function (Figure 3) [4,10].

A unifying hypothesis. Compelling evidence suggests that IBS results from interactions among environment, host and genetic factors. Different triggers (including diet, microbiota, bile acids, etc.) in genetically predisposed individuals may contribute to the loss of intestinal barrier function allowing the passage of antigens through the mucosal layer. This may elicit enteroendocrine and mucosal immune responses which induce neuroplastic changes and affect afferent and intrinsic nerves, leading to symptoms and pathophysiological features of IBS.

Therapy

The current therapeutic options for IBS are generally focused on the treatment of one or more of the predominant symptoms, including constipation, diarrhea, bloating or abdominal pain. An important aspect of any treatment regimen is represented by education and reassurance of patients about the benignity of their condition and by lifestyle and diet modifications. The establishment of a positive patient-doctor relationship, with acknowledging the disease, educating and reassuring the patient about the disease, is crucial to improve the treatment outcome. Current dietary options include low-FODMAP, gluten-free and lactose-free diets.

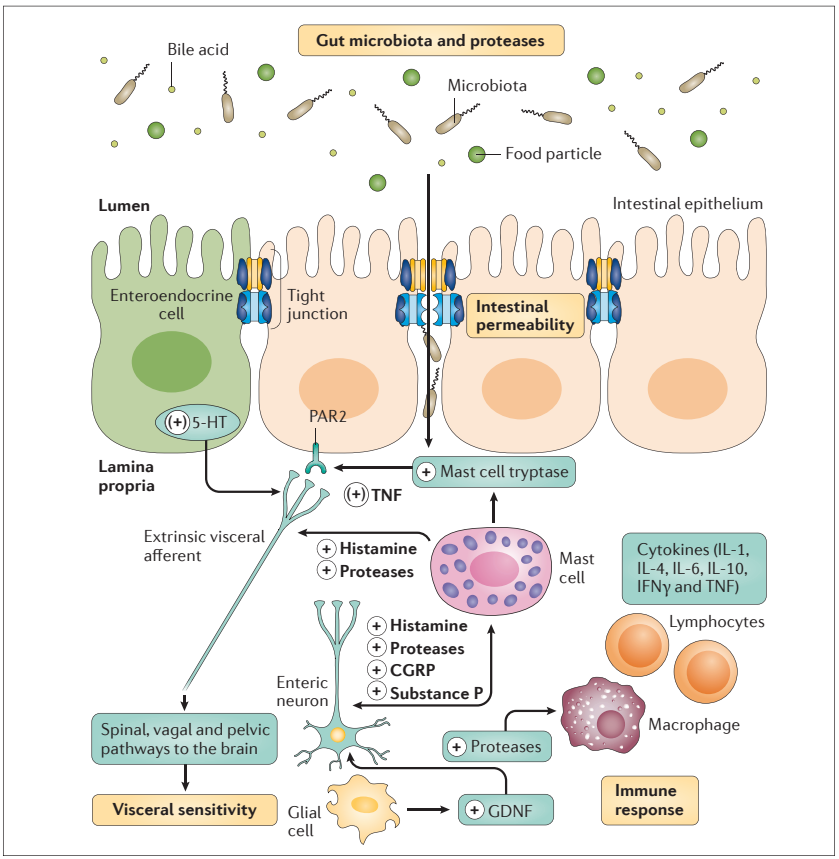

Figure 3: *Overview of the pathophysiology of IBS. Although the aetiology of irritable bowel syndrome (IBS) has not yet been completely elucidated, various factors have a role, including composition of the gut microbiota, intestinal permeability, immune cell reactivity and sensitivity of the enteric nervous system, the brain–gut axis (spinal, vagal or pelvic pathways) or the brain. The figure highlights those mediators that are probably involved in IBS pathology. The plus symbols indicate whether a mediator activates or inhibits its target cell; those in parentheses denote actions established in animal models and those without parentheses are effects demonstrated in humans (human tissue)*

5-HT: 5-hydroxytryptamine (also known as serotonin); CGRP: calcitonin gene-related peptide; GDNF: glial cell-derived neurotrophic factor; IL: interleukin; PAR2: proteinase-activated receptor 2; TNF: tumour necrosis factor

Drugs Mainly Targeting Abdominal Pain

In patients with predominant pain *antispasmodics* are often used as first-line treatment and meta-analyses support their efficacy. These drugs may act through anticholinergic action or smooth muscle relaxing activity, via different mechanisms (mainly calcium antagonism)[11]. Adverse effects mainly related to the anticholinergic activity of some drugs might limit their appeal. Peppermint oil, can be included among antispasmodics. It has calcium channel blocker, κ-opioid agonistic properties, anti-inflammatory effects, serotonergic antagonistic properties and analgesic properties that occur through activation of the temperature-sensing ion channel transient receptor potential cation channel subfamily M member 8 (TRPM8) [12].

Neuromodulators have also been largely used as second line treatments. Their effect is through the modulation of central nervous system function [13]. Meta-analyses support their efficacy, with a relatively low number-needed-to-treat (NNT) for antidepressants. Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRI) affect gastrointestinal motility through anticholinergic and serotonergic mechanisms and might therefore influence bowel habit disturbances in IBS. On the other hand, these adverse events can be of use in the modulation of bowel habit with TCA being preferred in IBS-D and SSRI in IBS-C [13].

Drugs Mainly Targeting IBS with Constipation

Osmotic laxatives, including polyethylene glycol (PEG), are often useful in clinical practice, as first line treatment [14]. Other agents that are commonly used include fiber supplements. There are several new options for the treatment of IBS-C and will be briefly described below.

Guanylate cyclase C agonists. Linaclotide is a 14-amino acid peptide luminally acting as an agonist of the guanylate cyclase receptor C (GC-C). Linaclotide administration improved colonic transit in a dose-dependent manner [15]. In pivotal studies in the USA in patients with chronic constipation (doses of 145 μg and 290 μg daily) and IBS-C (290 μg), linaclotide was shown to improve stool frequency and consistency and ease of defecation as well as abdominal pain, discomfort and bloating [16-18]. The most common adverse event in clinical trials was diarrhea, leading to discontinuation in some 5% of patients with IBS-C [16-18]. This drug is approved for treatment of IBS-C and chronic idiopathic constipation in many countries.

Plecanatide is a 16-amino acid peptide nearly structurally identical to uroguanylin, apart from the substitution of Asp^3 with Glu^3. Plecanatide acts as GC-C agonist and was developed for the treatment of chronic constipation and IBS-C. Plecanatide has shown efficacy over placebo in both chronic constipation and IBS-C at the doses of 3 mg or 6 mg [19-21]. Plecanatide is now approved in the USA for treatment of chronic idiopathic constipation and IBS-C.

Lubiprostone. Lubiprostone is a bicyclic fatty acid derived from prostaglandin E1 that acts by specifically activating ClC-2 chloride channels on the apical aspect of gastrointestinal epithelial cells, producing a chloride-rich fluid secretion in the lumen. Lubiprostone was approved in the USA in 2008 and is now available for the treatment of IBS-C in the US and other countries, based on the results of a pivotal study showing the its efficacy over placebo at a dose of 8 µg twice daily [22]. Adverse events included diarrhea (11%) and nausea (11%) which were usually mild but contributed to discontinuation in some patients (1.8%) [23].

Tenapanor. Tenapanor is a first in class small-molecule inhibitor of gastrointestinal Na+/H+ exchanger 3 (NHE3; also known as SLC9A3). Tenapanor dose-dependently increases intestinal fluid volume and transit through reduced absorption of sodium and phosphate [24]. In a phase 2, double-blind study, patients with IBS-C (Rome III criteria) were randomized (1:1:1:1) to receive tenapanor 5 mg, 20 mg, or 50 mg b.i.d., or placebo b.i.d. for 12 weeks. The 50-mg dose twice daily improved stool pattern, bloating and pain over placebo [25]. In a 12-week phase III study in IBS-C patients, tenapanor 50 mg twice daily met its primary end point on abdominal pain and increase in complete spontaneous bowel movements [26].

Agents acting on bile acid metabolism. Increasing colonic bile acid concentration has been evaluated as a treatment approach in IBS-C or in chronic constipation. The approaches included the use of chenodeoxycholate (CDC) in delayed-release oral formulation or the antagonism of the ileal bile acid transporter (IBAT; also known as SLC10A2) reducing the reuptake of bile acids in the terminal ileum[27]. CDC improved constipation and accelerated colonic transit in female patients with IBS-C [28], and an IBAT antagonist, A3309 or elobixibat, accelerated colonic transit [27] and improved constipation-related symptoms in patients with functional constipation in phase II trials [29,30].

Drugs Mainly Targeting IBS with Diarrhea

Poorly absorbable antibiotics. There is increasing evidence indicating that subgroups of patients with IBS have abnormal microbiota composition both in the colon and small intestine. Rifaximin is an oral, poorly absorbed, broad-spectrum antibiotic that targets the gut and is associated with a low risk of bacterial resistance. A large clinical trial in patients with non-constipation IBS demonstrated significantly higher proportions of patients achieved adequate relief of global IBS symptoms during the 10-week follow-up period with a therapeutic gain of 8-10%. As symptoms recur over time following initial treatment, a re-treatment trial with rifaximin was conducted. The results of this study showed that patients with IBS-D with relapsing symptoms showed that repetition of rifaximin treatment led to the same efficacy registered in the previous trial. In addition, rifaximin was safe and not associated with development of antibiotic resistance [31].

Opioid system modulators. For the treatment of diarrhea, the anti-diarrheal agent loperamide is commonly used in clinical practice, however clinical trials evaluating its effectiveness are lacking. Eluxadoline is a new mixed μ-opioid and κ-opioid receptor agonist and δ-opioid receptor antagonist developed for the treatment of IBS-D[32]. Two large phase III studies encompassing a total of 2,425 IBS-D patients assessed the efficacy of eluxadoline 75 mg and 100 mg twice daily versus placebo 137. In both studies, the composite pain and bowel habit end point response over 12 weeks with 75 mg and 100 mg was superior to placebo. The efficacy of eluxadoline was also shown in patients who self-reported either adequate or inadequate control of their symptoms with prior loperamide use [33].

Rare and transient severe adverse events in the phase III trials, including sphincter of Oddi spasm (eight patients; 0.5%) and pancreatitis (five patients; 0.3%) were recorded in the active treatment arms only [34]. These events were limited to patients who were chronic heavy alcohol abusers, had biliary sludge or history of cholecystectomy with sphincter of Oddi spasm [34,35]. For these reasons, the eluxadoline is contraindicated in alcohol abusers or in subjects who had a prior cholecystectomy. Eluxadoline is approved for treatment of IBS-D in the USA as well as in Europe.

Serotonin receptor modulators. Ramosetron is a novel 5-HT_3 antagonist which has been predominantly tested in IBS-D in Japan where it is approved and marketed. In a 12-week trial, ramosetron was found to be more effective than placebo in the treatment of IBS-D. In a trial in men ramosetron determined a therapeutic gain on stool patterns over placebo of 31,1%. In a trial in women there was a global therapeutic gain over placebo of 18,7%. The safety profile of ramosetron was excellent in these trials [36,37].

Ondansetron, is a relatively dated 5-HT_3 antagonists, which is widely globally available and initially developed for the treatment of chemotherapy-induced nausea and vomiting [38]. In a recent randomized, placebo controlled, cross-over trial in 120 patients with IBS-D, ondansetron improved stool consistency and urgency but did not improve abdominal pain scores [39].

Tachykinin receptor modulators. Ibodutant is a selective neurokinin-2 receptor antagonists which has been tested in a phase II study in IBS-D. This trial showed that ibodutant 10 mg was superior to placebo in women but not in men with IBS-D [40]. However, confirmatory phase III trials in Europe and USA failed to confirm its efficacy.

Agents acting on bile acid metabolism. Cholestyramine is the most frequently used bile acid binding agent to treat diarrhea. Nonetheless, cholestyramine use is often associated with gastrointestinal adverse events including abdominal pain, bloating, nausea and vomiting and constipation [41-43]. New bile acid binding agents include

colestipol and colesevelam that may be associated with fewer adverse events. Nonetheless their efficacy on diarrhea is not well documented [42-44]. Promising results have been reported with a novel colonic-release bile acid sequestrant, A3384, which has been tested in a pilot study in patients with bile acid diarrhea [45].

Farnesoid X-activated receptor (FXR; also known as NR1H4) reduces hepatic bile acid synthesis by stimulating FGF19 production. Several FXR agonists are under development, including *obeticholic acid* which improved stool form and symptoms of diarrhea in a proof-of concept study in 20 patients with primary and secondary bile acid diarrhea [46].

Conclusions

New drugs tested in controlled studies have provided additional ways to treat patients with FBDs and IBS. However, considerable unmet needs for effective and safe treatment remain. As IBS is a complex, heterogeneous and multifactorial disorder, a combination of management based on evidence together with a personalized treatment approach is advisable. Studies aimed at better understanding the pathophysiology of FGIDs along with the development of new drugs remain a challenge for the future.

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Neil H. Stollman

17:30 Diverticular Disease and Its Complications: from Guidelines to Clinical Practice

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Introduction

Diverticular disease accounts for over 2 million outpatient visits annually in the U.S. and is the most common gastrointestinal (GI) indication for hospitalization, accounting for $2.7 billion in costs [1]. It is also the most commonly reported finding at colonoscopy, identified in >40% of all exams and in more than 70% of patients older than 80 years. Further, both the incidence of, and rate of hospitalization for, seem to be increasing in both Europe and the United States [1]. Here we will review the recently published literature and new developments concerning the pathogenesis, risk factors and treatments of diverticular disease of the colon, with attention to the pathogenesis and treatment of acute diverticulitis as well as Symptomatic Uncomplicated Diverticular Disease (SUDD) (Figure 1) [2].

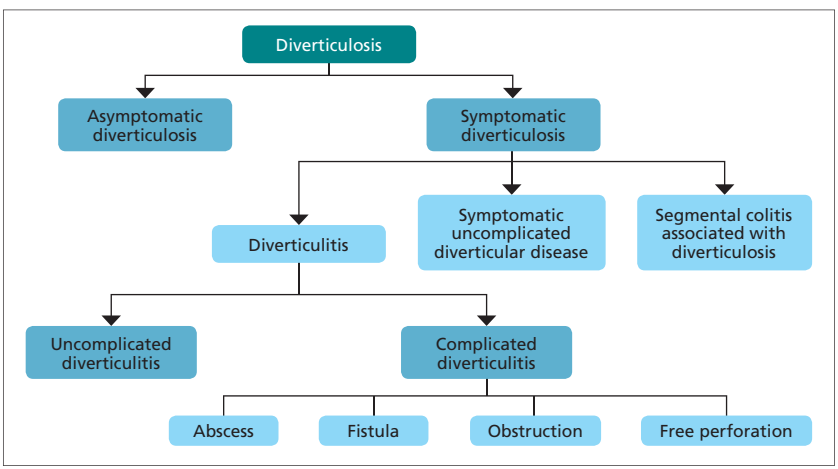


Figure 1: *Classification of diverticular disease (from Rezapour* et al. *[2])*

Dietary Fiber: Role in Pathogenesis and Treatment

The conception of diverticulosis as a 'fiber-deficiency' disease was originally suggested in seminal work by Burkitt and Painter [3], and has remained a widely accepted thesis for over forty years. Supportive observations included a lower rate of diverticulosis in populations with higher dietary fiber intake, e.g. Africa, compared with 'westernized' populations that were consuming lower fiber diets over time, coincident with increasing diverticular disease [4,5]. Further, vegetarians with higher dietary fiber intake have been reported to have lower rates of diverticulosis, and experimentally, rodents fed a very low fiber diet develop diverticulosis as well [6]. The thesis is also intuitively appealing, and has become fairly accepted dogma, despite shortcomings in the data available, including the assumption of uniform regional dietary habits, and the lack of control for regional differences in lifespan.

A recent study challenging this 'fiber deficiency' theory was published by Peery *et al.* [7], who performed an observational cross-sectional study of over 2000 patients undergoing colonoscopy, who underwent a telephone dietary history within three months after their colonoscopy. They observed that a high-fiber diet was actually associated with a greater, and not lower, prevalence of diverticulosis, as might have been expected. The relationship was dose-dependent, and strongest in those with more diverticula. Also, surprisingly, they reported that subjects with ***more*** frequent bowel movements had a great risk, although standard thinking would have suggested a greater risk in more constipated patients. No association with dietary fat or red meat intake, nor physical activity, was demonstrated. The validity of these conclusions has been questioned, due to a number of methodologic considerations, including that the authors only assessed ***current*** dietary history, which may not be reflective of dietary intake years or even decades earlier, when diverticulosis was developing. Further, subjects were aware of their diagnosis of diverticulosis, and could certainly have been instructed to increase their dietary fiber intake, or learned over time that increasing their dietary fiber intake, even if it had been low decades earlier, led to present day symptomatic improvement in potential diverticular symptoms.

While this important study calls into question the standard theory of low fiber diets ***causing*** diverticulosis, related and more clinically relevant questions concern the role of fiber in causing complications, or as ***treatment*** for patients with known diverticulosis. Aiming at these questions, two large prospective cohort studies have been reported with highly consistent and favorable results. The Health Professionals Follow-up study [8] followed over 47,000 men for four years and reported a relative risk for symptomatic disease in highest *versus* lowest fiber quintiles of 0.63 (95% CI, 0.44-0.91). The Oxford-EPIC cohort [9], following over 47,000 men and women in Europe, with 12 years of follow up, reported an adjusted relative risk for complications (hospitalizations or death) of 0.59 (95% CI, 0.46-0.78). The relative risk for vegetarians *versus* meat eaters was similar: 0.69 (95% CI, 0.55-0.86). Given the consistent evi-

dence from these cohort studies that fiber likely diminishes diverticular complications, and recognizing that it is complications, rather than the mere occurrence of diverticulosis that accounts for morbidity and costs, we should likely not yet be advising patients to avoid a higher dietary fiber intake, which likely has other salutatory health benefits as well.

Non-Steroidal Antiinflammatory Drugs

The recognition that non-steroidal antiinflammatory drugs (NSAIDs) are an important risk factor for upper GI bleeding has been well established. Multiple investigations and meta-analyses have also confirmed a consistent association between NSAID use and diverticular bleeding, with Odd Ratios (ORs) generally between 2 and 3. More recently, a large meta-analysis [10] evaluating 23 studies has confirmed the established bleeding risk with NSAIDs (OR 2.69), but has also described an increased risk of perforation or abscess with NSAIDs (OR 2.49), steroids (OR 9.08) and opioids (OR 2.52).

Genetics

Consistent with the prevailing 'fiber deficiency' hypothesis, the generally accepted belief was that diverticular disease was largely due to environmental factors, mainly a deficiency of dietary fiber. However, two recent twin registries, one from Denmark [11] and the other from Sweden [12], have reported consistent results, with relative risk (ranging from 7-15) of diverticular disease in one twin, when the other had diverticular disease. These studies have suggested that 40-53% of susceptibility to diverticular disease results from genetic factors.

Does Eating Seeds/Nuts Confer Any Risk?

For decades, patients with diverticular disease have been advised to avoid seeds and nuts, for fear that these particulates would 'clog' diverticula and foster diverticulitis. Lacking evidence in support of this belief, the American College of Gastroenterology (ACG) Practice Guidelines in 1999 stated that since "controlled studies that support this belief are lacking….there is no role for 'elimination' diet". In a landmark study, Strate *et al.* [13] reported on 47,000 men in the US Health Professionals Follow-up Study and found that nuts and popcorn, rather than increasing risk of diverticulitis, were either unrelated, or perhaps even protective, with an OR of 0.72-0.80. The most recent Guidelines from the American Gastroenterological Association (AGA) specifically suggests against advising patients with diverticulitis to avoid seeds and nuts [14].

Other Risk Factors

Beyond fiber, many other environmental factors are thought to influence the presence of diverticulosis and/or its complications, including the Western dietary pattern (high in red meat, refined grains, and high-fat dairy), obesity, smoking, physical inactivity, and alcohol (Table 1).

Table 1: Factors associated with increased risk of diverticulosis or its complications

Alcohol
Aspirin and other NSAIDs
Diets high in red meat ("Western dietary pattern")
Ethnicity*
Gender **
Genetics
Increasing age
Obesity
Physical inactivity
Residence in Western countries (e.g., United States, Western Europe, Australia)
Smoking
Vitamin D deficiency
* Caucasians have the highest prevalence of diverticulitis but African-Americans receive more operative intervention; African-Americans have the highest risk of diverticular bleeding
** Women have a modestly increased risk of diverticulitis *versus* men but men and women have equivalent risk of diverticular bleeding

Risk of Developing Acute Diverticulitis

For many years, reviews and book chapters and Society Guidelines have generally quoted a risk of developing diverticulitis in patients with incidentally diagnosed diverticulosis ranging from 10-25%. This consensus was based, however, on very limited and quite dated studies. Recently, a large (albeit retrospective) study [15] has reported data from the Los Angeles VA system, evaluating patients who underwent colonoscopy and were found to have diverticulosis. Over 11 year follow up, only about 4% developed diverticulitis based on fairly loose criteria; if stringent criteria were utilized, with computed tomography (CT) or surgical confirmation, only 1% developed. The 'ideal' prospective study to answer this question will be challenging to perform, but available evidence suggests that the risk is likely lower than we've previously thought.

Role of Antibiotics in the Treatment of Acute Diverticulitis

A notable shift in the treatment landscape of acute, uncomplicated diverticulitis has been occurring over at least the past decade. Standard antibiotic practice has been called into question: a 2012 Cochrane review [16] concluded that there was no dif-

ference between antibiotics and no antibiotics in uncomplicated diverticulitis and two large randomized clinical trials, totaling over 11 patients – the AVOD trial [17] and the DIABOLO trial [18] – showed that antibiotics for acute, uncomplicated diverticulitis do not accelerate recovery. AVOD also showed that antibiotics do not prevent complications or recurrence. And indeed, the most recent AGA Guidelines [14] suggest selective, rather than routine, use of antibiotics in acute uncomplicated diverticulitis, a position echoed by many European Guidelines [19,20].

Role of Surgery in Acute Diverticulitis

Prior Guidelines from both the American Society of Colorectal Surgery [21] and the American College of Gastroenterology [14] had both previously recommended consideration of an elective, prophylactic surgical resection after a *second* confirmed attack of acute diverticulitis. Newer data questioning this assumption, with a more recent Markov Model from a Washington State database [22] suggesting that surgical intervention after a 4th (rather than 2nd) episode led to 0.5% fewer deaths and >$1000 saved. The most recent American Society of Colon and Rectal Surgeons (ASCRS) [21] recommendations have echoed this, now advocating that "the number of attacks of uncomplicated diverticulitis is not necessarily an overriding factor in defining the appropriateness of surgery" and suggesting this discussion be made on a more individualized case-by-case basis. This position was also adopted by the recent AGA Guidelines [14].

Symptomatic Uncomplicated Diverticular Disease

Patients who come to clinical attention because of nonspecific abdominal complaints are commonly found to have diverticulosis; if the two are felt to be related, and in the absence of objective findings of acute diverticulitis, the entity is often termed SUDD. The true prevalence of SUDD is unknown, as prior literature has primarily focused on diverticulitis and diverticular hemorrhage. Further, clinical similarities between SUDD and Irritable Bowel Syndrome (IBS) confound our ability to epidemiologically distinguish the two entities. Indeed, like IBS, it is commonly held that SUDD typically runs a long-term, benign course and portends a low incidence of complications.

The pathophysiology of SUDD is not well defined. Some authorities have postulated that diverticula are, in fact, a late consequence of IBS. In a Danish cohort [23] of IBS patients, one third of whom had diverticula, no difference in symptoms or prognosis was detected between those with diverticula and those without diverticula over more than 5 years of follow-up. Further highlighting this consideration, Ritchie *et al.* [24] reported that there was a similarity of pain sensation from rectal balloon distention in patients with IBS and those with diverticulosis. A recent retrospective study [25] reported that in patients without prior diagnosed functional bowel disease, IBS was 4.7 times more likely to develop after an index episode of diverticulitis, and the authors posit a 'postdiverticular IBS' akin to 'postinfectious'. Similar to the IBS literature, multi-

ple factors are postulated to play contributing roles: visceral hypersensitivity (inflammatory damage to enteric nerves and aberrant re-innervation), altered colonic motility, subacute obstruction, due to fibrosis or hypertrophy, an altered intestinal microbiota and low-grade chronic inflammation, as evidenced by elevations of inflammatory markers (such as fecal calprotectin), as demonstrated in a recent paper from Italy [26], as well as Substance P, VIP, neuropeptides, TNF, galanin, and neurokinins.

The suggestion of shared pathophysiologic paradigms for SUDD and IBS provides the basis for treatment options. For decades, fiber has been a mainstay of treatment for SUDD, although this practice is based on weak evidence. Further, the literature provides little guidance as to the type and quantity of fiber needed. It is notable that bran fiber can increase flatulence and actually worsen symptoms in some patients. Data from the IBS literature [27,28] suggest that soluble fiber (psyllium) is superior to insoluble fiber (bran) in improving symptoms.

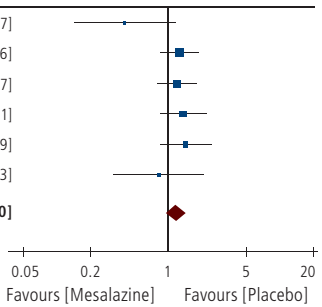
The assumption of underlying inflammation in patients with SUDD underlies investigations of 5-ASA compounds, a well-established and first-line therapy for inflammatory bowel disease (IBD). Notably, in a case series of over 900 Mayo Clinic patients undergoing surgery for SUDD, [29] 76% of cases had evidence of acute or chronic inflammatory changes. The DIVA study [30], a randomized trial comparing 12 weeks of mesalamine 2.4 g/day with placebo after CT-confirmation of acute diverticulitis, demonstrated a consistent trend towards decreased SUDD symptoms, but was underpowered to detect differences in recurrent diverticulitis (there was no difference indeed). A systematic review of 6 randomized clinical trials including 1021 patients [31] reported that mesalazine was more effective than placebo or other therapies in achieving symptom relief in patients with SUDD. It is notable, however, that there was significant heterogeneity amongst the trials, with differing endpoints, dosing, and modality of treatments (i.e. continuous vs. cyclical). A much larger trial [32], with over 1000 subjects, recently failed to demonstrate any reduction in acute diverticulitis, a conclusion reached also by a very recent meta-analysis (Figure 2] [33]. 5-ASA derivatives are a promising therapy for SUDD, although further high-quality placebo-controlled trials supporting its efficacy will be needed before widespread use can be recommended in this population, and it is overtly not recommended for prevention of acute diverticulitis, a different endpoint.

It has been postulated that disturbances in the intestinal microbiota might predispose to inflammation. And using this rationale, rifaximin, a non-absorbable antibiotic with broad-spectrum activity, has been studied in SUDD with optimistic results, including reduction in frequency and severity of symptoms. In a meta-analysis of 4 randomized controlled trials studying patients with SUDD [34] the combination of rifaximin with fiber was 29% more effective than placebo in obtaining symptom relief at 1 year. The number needed to treat (NNT) for this benefit was 3. An open-label, proof-of-concept study [35] compared the efficacy of high-fiber supplementation (3.5 g b.i.d.), with

or without 1 week per month of rifaximin (400 mg b.i.d.) for 1 year on secondary prevention of diverticulitis. Recurrences occurred in 10.4% of patients given rifaximin plus fibers *versus* 19.3% of patients receiving fiber alone.

Study or Subgroup	Mesalazine Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Parente 2013	6	45	13	47	4.3%	0.40 [0.14, 1.17]
PREVENT 1 014	178	436	52	147	28.2%	1.26 [0.85, 1.86]
PREVENT 2 2014	161	444	46	142	26.7%	1.19 [0.79, 1.77]
SAG 37 2017	53	165	43	168	19.7%	1.38 [0.85, 2.21]
SAG 51 2017	83	162	34	81	15.8%	1.45 [0.85, 2.49]
Stollman 2013	11	40	13	41	5.3%	0.82 [0.31, 2.13]
Total (95% CI)		**1292**		**626**	**100.0%**	**1.20 [0.96, 1.50]**
Total events	492		201			

Heterogeneity: Tau² = 0.01; Chi² = 5.48, df = 5 (P = 0.36); I² = 9%
Test for overall effect: Z = 1.60 (P = 0.11)



(The solid squares denote the odds ratio, the horizontal lines represent the 95% confidence intervals and the diamond denotes the pooled OR)

Figure 2: *Forest plots of the comparisons of diverticulitis recurrence (from Khan* et al. *[33])*

Also based on presumptive dysbiosis, probiotics have been studied, with some benefit shown in trials involving bacterial strains such as *Escherichia coli, Lactobacillus casei, Bifidobacterium infantis,* and combination products such as VSL#3, but such trials are generally small and lack a placebo group. Although higher-quality evidence needs to be produced to support this approach [36], the microbiome is likely to become an important target for therapy in SUDD in coming years.

Surgical intervention should not be routinely considered for patients with uncomplicated diverticulosis, because the risks of surgery outweigh its benefits in most cases, but some patients chose resection due to ongoing smoldering pain. In the previously mentioned cohort of over 900 Mayo Clinic [29] SUDD patients who underwent sigmoid resection with primary anastomosis for their symptoms, 76.5% had complete resolution of their symptoms, with 88% of patients being pain free after 1 or more years of follow-up (Table 2).

Table 2: Key Recommendations (from Rezapour *et al.* [2])

In addition to dietary fiber intake, genetics plays a role in the pathogenesis of diverticular disease
Antibiotic use should be selective in acute uncomplicated diverticulitis, consider withholding in mild cases
Colonoscopy should be performed after resolution of acute diverticulitis if high-quality exam of the colon has not been recently performed
Fiber intake decreases diverticular disease complications
NSAIDs should be avoided in patients with a history of diverticulitis; seeds and nuts need not be

NSAIDs: nonsteroidal antiinflammatory drug

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Stephen B. Hanauer

18:00 Management of IBD: What the Future Holds

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Introduction

Prediction is very difficult, especially if it's about the future
– Nils Bohr, Nobel laureate in Physics –

Inflammatory Bowel Disease (IBD) is complicated and remains "idiopathic" with an incomplete understanding of etiopathogenesis. Similar to other immune-mediated inflammatory diseases (e.g. rheumatoid arthritis, psoriasis, etc.) genetic, epigenetic, environmental (including diet and the microbiome), and immune factors contribute to the heterogeneous patterns and phenotypes in, as yet, incompletely understood patterns [1,2].

In IBD, precision (personalized) medicine, the tailoring of medical treatment to the individual characteristics of each patient, and, the science of individualized prevention and therapy are still in their infancy. Evidence gaps remain regarding diagnosis, prognosis, clinical and treatment targets and biomarkers, to date, remain general and non-specific (e.g. C-reactive protein and calprotectin). Biomarkers have failed to meet classic qualities of: simplicity, accuracy, minimally invasive, inexpensive, rapid, and reproducibility.

Furthermore, they are encumbered by low sensitivity/specificity and low prognostic/predictive values and lack validation in independent cohorts while evaluation of the microbiome remains in its infancy [3].

Diagnostic challenges include pre-clinical (genetics/epigenetics, serologies, microbial) predictors of clinical phenotypes and prognosis. The evolving field of "-omics" research has also been challenged by high costs for validation of unbiased omics testing, confounding outcome measures (disease activity, duration, location, drug effects, study design, and heterogenous cohorts), selection bias based on convenience sampling, lack of support from pharmaceutical companies, and reluctant adoption by physicians and patients [3].

Current Biologic Therapies

TNF Inhibitors

Pharmacology

Since the introduction of infliximab for Crohn's disease (CD) in 1998, TNF inhibitors have become widely used in moderate-to-severe IBD. TNF is produced by T-lymphocytes and macrophages [4,5].

Binding of TNF to its receptor leads to increased expression of pro-inflammatory cytokines (Figure 1) [6]. Multiple mechanisms of action potentially contribute to the effectiveness of anti-TNF agents, including neutralization of circulating TNF, inhibition of TNF binding to its receptor, and reverse signaling [7].

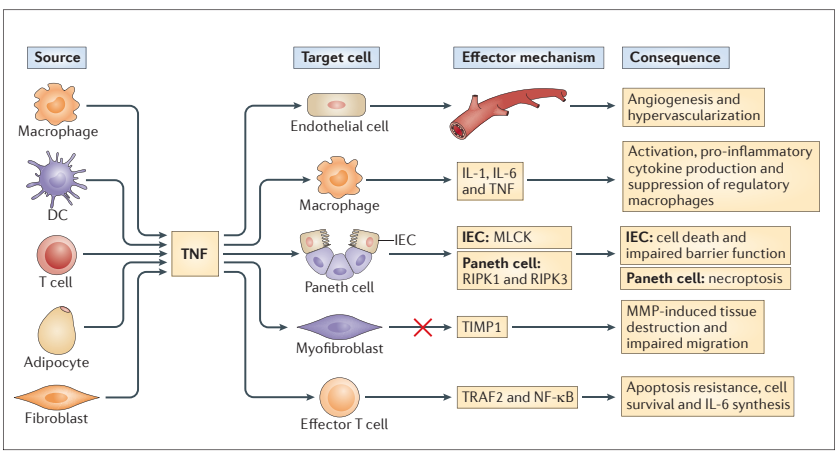

Figure 1: *Central role of tumour necrosis factor in the pathogenesis of IBD. In IBD, increased amounts of soluble and membrane-bound tumour necrosis factor (TNF) are produced by various immune and stromal cell populations, such as macrophages, dendritic cells (DCs), effector T cells, adipocytes and fibroblasts. TNF has been shown to exert various pro-inflammatory functions in the inflamed mucosa in IBD. In particular, TNF induces hyper- vascularization and angiogenesis, augments pro-inflammatory cytokine production by macrophages and T cells, causes barrier alterations and promotes cell death of intestinal epithelial cells (IECs) and Paneth cells. TNF also promotes tissue destruction by increasing the production of matrix metalloproteinases (MMPs) by myofibroblasts and drives T cell resistance to apoptosis via the induction of TNF receptor-associated factor 2 (TRAF2) and the activation of nuclear factor-κB (NF-κB). TNF-specific antibodies may alleviate disease by simultaneously suppressing several pro-inflammatory pathways in patients with IBD. IL, interleukin; MLCK, myosin light chain kinase; RIPK, receptor-interacting protein kinase; TIMP1, tissue inhibitor of matrix metalloproteinases (from Neurath [5])*

Infliximab, adalimumab, and golimumab are IgG1 monoclonal antibodies that can cross the placenta. Certolizumab differs in that it is a pegylated Fab fragment and is unable to cross the placenta due to lack of an Fc portion. Biosimilars to infliximab and adalimumab have been developed and are highly similar, but not identical, in structure to the originators [8].

The pivotal role of TNF in killing of intracellular pathogens is associated with the risk of activation of tuberculosis, histoplasmosis, and similar pathogens. TNF inhibitors are contra- indicated in the setting of significant infections and have been associated with an increased risk of pneumonias [9].

The half-life of anti-TNF monoclonal antibodies is approximately 14 days [10]. Monoclonal antibodies are cleared, primarily, by the reticuloendothelial system. A number of factors have been identified that increase clearance in the setting of IBD including gender, body mass index, severity of inflammation (blood and tissue TNF levels, C-reactive protein (CRP), and fecal calprotectin), albumin concentrations, concomitant steroids and immunosuppressives, and the presence of anti-drug antibodies [10,11]. In addition, it has recently been recognized that patients with severe ulcerative colitis (UC) also clear monoclonal antibodies in the stool due to blood and protein exudation [12]. The importance of drug levels has led to increasing use of TDM of TNF inhibitors in IBD [13].

Clinical Use and Optimization

Infliximab, adalimumab, and golimumab are approved for use in induction and maintenance of remission in UC. In the ACT 1 and 2 trials, 5 or 10 mg/kg of infliximab was superior to placebo when evaluating clinical remission and mucosal healing at weeks 8, 30, and 54 [14]. In ULTRA 1 and 2, adalimumab significantly increased rates of remission in UC patients as compared to placebo up to week 52 [14,15] and, in the PURSUIT trial, golimumab was superior to placebo in inducing clinical response at week 6 and maintaining remission at weeks 30 and 54 [16,17].

In ASUC, infliximab is the primary treatment for rescue therapy. Infliximab is administered based on weight (5–10 mg/kg). High-dose infliximab (10 mg/kg) may be used to overcome the fecal loss of infliximab in ASUC [12]. In patients who do not respond to an initial dose of infliximab, accelerated infliximab dosing may be used. In a small study of 50 patients with ASUC, accelerated infliximab induction with three doses within 4 weeks significantly decreased the need for early colectomy [18]. A recent abstract evaluating the 30-day colectomy rate in patients with high-dose infliximab (10 mg/kg) found that an initial dose of infliximab 10 mg/kg decreased the risk of colectomy (odds ratio [OR] 0.137; 95% CI 0.04–0.46) [19].

In CD, infliximab, adalimumab, and certolizumab are approved for use in induction and maintenance of remission (Table 1).

Table 1: Biologic dosing in IBD (from Chang & Hanauer [20])

Medication	Disease treated	Route of administration (IV, SC, PO)	Dose
Infliximab	UC and CD	IV	Induction: 5–10 mg/kg (weeks 0, 2, and 6) Maintenance: 5–10 mg/kg every 4–8 weeks
Adalimubab	UC and CD	SC	Induction: 160 mg (week 0), 80 mg (week 2) Maintenance: 40 mg every 7–14 days
Golimumab	UC	SC	Induction: 200 mg (week 0), 100 mg (week 2) Maintenance: 100 mg every 4 weeks
Certolizumab	CD	SC	Induction: 400 mg (weeks 0, 2, and 4) Maintenance: 400 mg every 4 weeks
Vedolizumab	UC and CD	IV	Induction: 300 mg (weeks 0, 2, and 6) Maintenance: 300 mg every 4–8 weeks
Ustekinumab	CD[a]	IV – SC	Induction: <55K: 260 mg 55-85 kg: 390 mg >85 kg: 520 mg Maintenance: 90 mg every 8 weeks
Tofacitinib	UC	PO	10 mg twice daily[b]
Mongersen	CD	PO	40 or 160 mg daily[c]

SC: subcutaneous; PO: oral; UC: ulcerative colitis; CD: Crohn's disease
a Clinical trials ongoing in UC
b OCTAVE trials, not commercially available [81]
c Clinical trial data not commercially available

In the ACCENT 1 trial, patients with moderate-to- severe CD who responded to an initial infliximab dose of 5 mg/kg were then randomized to receive subsequent doses of infliximab or placebo at weeks 2, 6, then every 8 weeks. At week 30, patients receiving infliximab were more likely to be in remission compared to placebo (OR 2.7; 95% CI 1.6–4.6) [21]. The CHARM trial confirmed that adalimumab treatment in CD was superior to placebo in producing a clinical response at week 4 and maintenance of remission out to week 56 [14]. In the PRECISE trials, CD patients receiving certolizumab had higher remission rates at week 26 compared to placebo [14]. Comparing efficacy of TNF inhibitors is difficult as there are no high-quality, head-to-head trials. In a real-world, retrospective, comparative effectiveness database study of 3205 biologic naive CD patients, infliximab treated patients had a lower risk of CD-related hospitalization, abdominal surgery, and corticosteroid use when compared with adalimumab treated patients [23]. Compared to certolizumab treated patients,

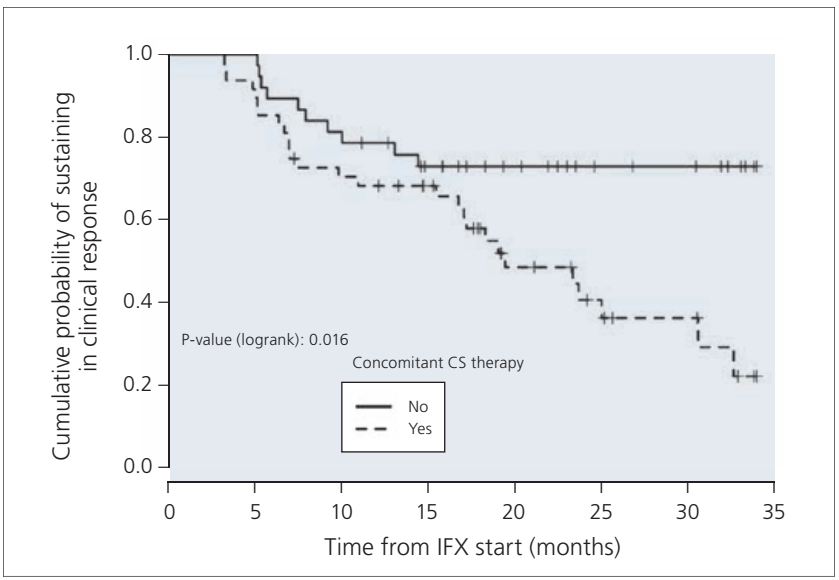

Figure 2: *Sustained clinical response to infliximab (IFX) stratified by IFX trough levels and concomitant treatment with corticosteroids (CS) at IFX start (from Bortlik* et al. *[33])*

infliximab-treated patients also had lower rates of all-cause hospitalization. Adalimumab and certolizumab outcomes were comparable. In UC, a similar real-world, retrospective, database study of 1400 UC patients comparing infliximab and adalimumab found no difference in risk of hospitalization or serious infections. However, the authors did find that infliximab treated patients had significantly lower risk of corticosteroid use compared to adalimumab treated patients (hazard ratio [HR] 0.82, 95% CI 0.69–0.99) [24]. These data suggest that *at currently recommended doses*, there may be some benefit to using infliximab over the other biologic TNF inhibitors, but more definitive data, comparative effectiveness studies, and targeted dosing studies are required to truly differentiate pharmacodynamic effects. Trials of higher-dose adalimumab for both UC and CD are currently underway to determine optimal effectiveness.

In recent years, combination therapy of biologic TNF inhibitors with immunomodulators has received much attention. Combination therapy with infliximab and a thiopurine has been shown to be superior to monotherapy with infliximab or thiopurines alone

for clinical remission in both UC and CD [25,26]. Similar augmentation of clinical response has not been seen with infliximab and MTX combination therapy in the COMMIT study in CD that mandated steroid induction [27]. However, there is a notable decrease in immunogenicity, and hence increased drug concentrations, in CD patients receiving combination therapy with MTX [27,28].

Use of immunomodulators is known to increase the durability of biologics and decrease immunogenicity, thereby increasing drug levels (Figure 2) [29–33]. Ungar *et al.* recently described the addition of immunomodulators (thiopurines and MTX) in patients with antibodies to adalimumab [34]. In approximately half the patients, antibodies to adalimumab were able to be eliminated. Whereas previous theories supported synergistic mechanisms as the chief benefit of combination therapy, recent research suggests that combination therapy is successful mainly in decreasing immunogenicity and increasing biologic drug levels [32].

Therapeutic monitoring of TNF inhibitor drug levels and anti-drug antibodies has become an important tool to optimize therapy in IBD [13]. To date, most studies associating therapeutic responses with drug levels have been retrospective, and differing assays have been used to determine *optimal* TLs, with wide ranges of levels defined for UC and CD [35]. The utility of TLs has been most consistently assessed in determining mechanisms for loss of response to biologic agents. Patients with secondary loss of response with low trough drug levels and no anti-drug antibodies respond to dose escalation, whereas patients with low trough drug levels due to anti-drug antibodies respond to switching to an alternative anti-TNF [36]. Patients who lose response to an anti-TNF despite adequate trough concentrations require substitution to an agent with a different mechanism of action.

Data regarding prospective monitoring to *prevent loss* of response are less robust. A TL greater than 5 µg/ml has been associated with an increased likelihood of remaining on infliximab as compared to TLs less than 5 µg/ml (HR 0.3; 95% CI 0.1–0.6) [32]. In a study focusing only on CD patients, TLs greater than 3 µg/ml at the start of maintenance therapy predicted a sustained response to infliximab [33]. TLs of infliximab greater than 5 µg/ml and adalimumab greater than 4.9 µg/ml and 7.1 µg/ml have been associated with mucosal healing [37,38]. When focusing solely on perianal CD, TLs of 9.25 and 7.25 µg/ml at weeks 2 and 6, respectively, during infliximab induction have been associated with fistula response [39]. More evaluation is needed to define *optimal* levels (may differ between CD and UC) and inter-assay comparisons, but proactive, TDM with dose optimization is recommended.

Pharmacologic optimization of biologics with TDM may improve outcomes, but the data thus far have been mixed. In the TAXIT trial, UC and CD patients were initially optimized to achieve a minimal trough concentration (3–7 µg/ml) and then managed

either by clinical symptoms or by goal TLs [40]. At the end of 1 year of follow-up, though there was no difference in clinical remission rates, there were less flares and infusion reactions in the TL group. The difference in TAXIT groups may have been more apparent because of the lack of an initial optimization period. In the TAILORIX trial evaluating drug concentration (goal TL>3) *versus* symptom-driven infliximab maintenance dosing in patients with active CD on combination therapy, there was no difference in steroid-free clinical remission between groups at 1 year [41]. However, important endoscopic, pharmacokinetic, biomarker, and immunogenicity data from the TAILORIX trial are not yet available.

In conclusion, the biologic TNF inhibitors are a mainstay of therapy in IBD patients with moderate-to-severe disease, with or without immunomodulator therapy. TDM is a valuable tool for optimizing therapy. However, optimal drug levels for clinical remission and mucosal healing in specific IBD subgroups are still being defined. Potentially higher TLs are needed for healing of perianal fistulizing disease.

Anti-integrins

Pharmacology

Natalizumab and vedolizumab are monoclonal antibodies targeting adhesion molecules, thereby impairing lymphocyte trafficking to the gut. Natalizumab is a monoclonal antibody that binds to the integrin subunit α4 on lymphocytes, thereby inhibiting both α4β7, which binds to the MadCam addressin (mucosal adhesion molecule) in the gut, and α4β1, which binds to VCam (vascular adhesion molecule) throughout the body, including the gut and the central nervous system [42]. Despite being approved by the US FDA for use in CD, natalizumab has not been widely adopted due to the associated risk of progressive multifocal leukoencephalopathy (PML) [43]. Vedolizumab, approved in 2014, specifically inhibits α4β7 that is limited to 3% of circulating lymphocytes directed to the gut mucosa, thereby avoiding the risk of PML. Vedolizumab maximally saturates α4β7 receptors at doses starting at 2 mg/kg [44]. The half-life is approximately 25 days, somewhat longer than the anti-TNF monoclonal antibodies.
In contrast to TNF inhibitors, treatment with vedolizumab has not been associated with an increased risk of serious infections or neoplasia [42].

Clinical Use and Optimization

In UC, vedolizumab is effective in induction and maintenance of remission. In the GEMINI trials, adults with active UC who failed alternative treatments were administered induction doses of 300 mg IV at weeks 0, 2, and 6 [45]. Patients who responded to induction therapy were then randomized to receive either vedolizumab every 4 weeks, every 8 weeks, or placebo. At week 6, clinical response rates were 47.1% *versus* 25.5% for vedolizumab *versus* placebo patients, respectively. Though remission rates for vedolizumab *versus* placebo (16.9% *versus* 5.4%) were low, rates of mucosal healing were significantly higher with vedolizumab than placebo (40.9% *versus*

24.8%). A post-hoc analysis of week 6 data found that patients naive to biologic TNF inhibitors exhibited higher levels of clinical response compared to non-responders to TNF inhibitors (53% *versus* 39%) [46]. At week 52, patients on vedolizumab every 4 or 8 weeks (44.8% or 41.8%, respectively) were significantly more likely to be in clinical remission compared to patients on placebo (15.9%). In a long-term extension and safety study, maintenance of remission for responders to vedolizumab persisted at 2 and 3 years [47]. In patients receiving maintenance vedolizumab every 8 weeks who lost response prior to week 52, increasing vedolizumab administration frequency to every 4 weeks increased response and remission rates from 19% to 41%.

In CD, vedolizumab is modestly effective for induction of remission, but there is delayed efficacy. In GEMINI 2, patients with active CD and objective markers of inflammation were induced with vedolizumab. At week 6, clinical remission rates were low but significantly higher in the vedolizumab group compared to placebo (14.5% *versus* 6.8%) [48]. In GEMINI 3, CD patients who were TNF inhibitor non-responders had no difference in clinical remission rates at week 6 compared to placebo (15.2% *versus* 12.1%). However, when reevaluating at week 10, clinical remission rates were significantly higher in the vedolizumab group compared to placebo (26.6% *versus* 12.1%) [44]. Assessment of real-world efficacy at week 14 has been reported to be better than GEMINI trial data [49].

Vedolizumab for maintenance of remission in CD is effective. From the GEMINI trials, clinical remission rates at week 52 were 21.6%, 36.4%, and 39% for placebo, 4-week, and 8-week dosing, respectively [48]. Long-term safety registries show efficacy in maintenance of remission up to 3 years after induction therapy [49]. As echoed in the UC long-term safety data, CD patients who lost response with every 8-week dosing were able to achieve clinical remission at week 52 with every 4-week dosing in 32% of patients [50]. Thus, vedolizumab is a viable option for the long-term maintenance therapy in CD.

Vedolizumab drug and antibody levels are now commercially available, but the optimal target levels for vedolizumab have not been validated. In a small, prospective, observational study of IBD patients (31 CD and 16 UC) undergoing standard vedolizumab induction, week 6 TLs below 19 µg/ml were associated with a need for more frequent dosing (every 4 weeks) rather than the standard dosing (every 8 weeks) within 6 months [51]. All patients who received dose optimization with every 4-week dosing exhibited a clinical response. In a vedolizumab maintenance study of 113 IBD patients, there was a greater likelihood of being in remission if the vedolizumab level was greater than 10.9 µg/ml (OR 2.65; 95% CI 1.24–5.66) [52].

The rate of occurrence of antibodies to vedolizumab is low, approximately 3.5% [51,52].

Since its approval in 2014, vedolizumab has been integrated into the IBD armamentarium for use in the induction and maintenance of remission in UC and CD, particularly in patients with advanced age, history of malignancy, or prior biologic TNF inhibitor failure. In the GEMINI trials, vedolizumab dosing every 4 weeks resulted in similar efficacy as dosing every 8 weeks. However, in patients losing response to vedolizumab, increasing the frequency of dosing from every 8 weeks to every 4 weeks recaptures response in one-third of patients. The optimal vedolizumab drug level target has not yet been defined. Antibodies to vedolizumab are low, and the need for immunomodulator therapy for preventing immunogenicity is not clear.

Anti-IL-12/23

Pharmacology

Ustekinumab is a human IgG1 monoclonal antibody that blocks the p40 subunit that is common to IL-12 and IL-23, thereby inhibiting the downstream inflammatory cascade (Figure 3) [53,54]. Ustekinumab has been highly efficacious for the treatment of psoriasis and recently, at higher doses, for the treatment of CD. The elimination half-life of ustekinumab is approximately 3 weeks [52]. The initial induction dose of ustekinumab for CD is weight-based (Table 1). In contrast to other injectable biologics, the first dose of ustekinumab is administered intravenously due to evidence of improved clinical outcomes from an early trial [54]. Subsequent doses in CD are standardized at 90 mg subcutaneously every 8 weeks.

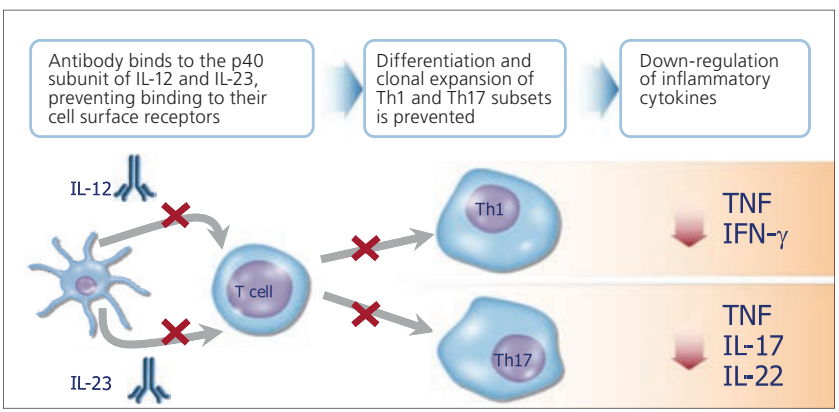

Figure 3: *Ustekinumab mechanism of action*

Despite the inhibition of downstream signaling, ustekinumab has not been associated with an increased risk of serious infections or neoplasia [53].

Clinical Use and Optimization

Currently, ustekinumab is only approved in IBD for use in CD. In the CERTIFI trial, CD patients receiving ustekinumab 6 mg/ kg exhibited a significantly greater clinical response as compared to placebo at week 6 (39.7% *versus* 23.5%) [55]. Lower concentrations of weight-based dosing did not result in significant clinical responses compared to placebo. At week 22, clinical remission rates were higher with ustekinumab than placebo (41.7% *versus* 27.4%). In UNITI-1, primary or secondary non-responders to TNF inhibitors had a significant clinical response at week 6 with 130 mg or 6 mg/kg when compared to placebo (34.3% or 33.7%, *versus* 21.5%) [22]. In the IM-UNITI maintenance trial, patients receiving subcutaneous ustekinumab every 8 or 12 weeks exhibited significantly higher rates of remission in the ustekinumab groups (53.1% and 48.8%, respectively) at week 44 as compared to placebo (35.9%). Changes in Crohn's Disease Activity Index (CDAI) and CRP started to become appreciable at week 20 and week 8, respectively [22].

Ustekinumab drug and antibody level data are available from the UNITI trials. Notably, drug levels are higher in patients induced with weight-based 6 mg/kg compared to 130 mg (6.4 *versus* 2.1 µg/ml) [22]. Drug levels were three times higher if patients received drug every 8 weeks rather than every 12 weeks. Finally, higher ustekinumab drug levels correlated with clinical remission. Most likely due to the longer half-life, the rate of formation of antibodies to ustekinumab (2.3%) is low.

Ustekinumab is the newest mechanism of action available for use in CD and is effective in induction and maintenance of remission, including in patients previously failing biologic TNF inhibitors. The UNIFI study is in progress and will provide data on induction and maintenance of remission in UC [56]. As with the biologic TNF inhibitors, data suggest that higher ustekinumab drug levels increase the likelihood of remission. The rate of ustekinumab antibody formation is low, and the need for immunomodulators to prevent immunogenicity is uncertain at this time. Based upon the potential efficacy and safety of targeting IL-23 without IL-12, trials of monoclonal antibodies that inhibit the p19 subunit are currently underway [57].

Limitations of Current Therapies

Our current approaches based on genetics, environment, immune system and microbial therapies have had variable effectiveness although there are examples of success, particularly regarding the genetics of monogenic early onset CD [58]. We have, indeed, learned how to cause IBD (e.g. check-point inhibitor therapies) [59] but cures remain elusive. Clues towards pathogenesis continue to emphasize genetic/epigenetics and the microbiome [60].

Our *treat to target concepts* [61] have had limited success with less than 50% of patients responding to any individual therapy to induce *mucosal healing* and even with intensive

escalation of therapies. Most often, evaluation of therapeutic approaches occurs late in disease progression after complications have already ensued [62]. Few studies have focused on early onset or post-operative disease before the evolution to fibrosis or fistulization that have eluded effective approaches.

However, recent evolution away from randomized, placebo-controlled trials towards comparative effectiveness or cluster randomization approaches that include a treat to target strategy have provided some optimism regarding improving therapeutic effectiveness in real world data compared with traditional phase III regulatory studies that determine efficacy in more homogeneous populations. Again, treatment of early, less complicated disease has been more effective than treating late disease as the "step up/top down" [63], "SONIC" [64], "REACT" [65], and "CALM" [66] studies have demonstrated. In contrast, treating to therapeutic drug levels as targets, while useful in assessing loss of response to biologics, has yet to be translated into effective prospective strategies [67].

Near Future Approaches

Tofacitinib

Pharmacology

Tofacitinib is an oral, small-molecule, Janus kinase (JAK) inhibitor being evaluated for use in UC [68]. Currently, tofacitinib is approved for use in rheumatoid arthritis. Tofacitinib inhibits all four isoforms (JAK 1, 2, 3, and TYK2), but has greater selectivity for JAK 1 and 3 [69]. Inhibition of the JAK pathway leads to downstream inhibition of cytokines including interferon-gamma (IFN-γ), IL-6, IL-12, and IL-23. There is good oral bioavailability of tofacitinib (74%), and the half-life is approximately 3 h such that twice-daily dosing provides stable drug concentrations

Clinical Data

Trials are ongoing to evaluate the efficacy of tofacitinib in UC. In 2012, Sandborn *et al.* evaluated the efficacy of tofacitinib in 194 adult patients with moderate-to-severe UC. Four doses were evaluated: 0.5, 3, 10, and 15 mg [70]. The 15 mg group had a significantly better clinical response compared to placebo (78% *versus* 42%). There was a dose–response relationship up to 10 mg. Endoscopic remission was also significant in the 3, 10, and 15 mg groups as compared to placebo. From these results, the OCTAVE trials evaluated tofacitinib 10 mg doses twice daily in adult UC patients. Tofacitinib had significantly greater efficacy in remission and mucosal healing end points as compared to placebo in preliminary abstract data [71]. Of interest, patients previously exposed to anti-TNFs exhibited similar efficacy as TNF-naive patients. Finalized data from this trial are pending.

Due to its immunosuppressive effects, tofacitinib has been associated with an increased risk of opportunistic infections, in particular herpes zoster [69].

Similar to tofacitinib, filgotinib is another JAK inhibitor with high selectivity for JAK1 over JAK2 and TYK2 [69]. Filgotinib is currently being studied in CD. Results for this trial are not yet available.

Mongersen

Pharmacology

Mongersen is a 21-base antisense oligonucleotide that blocks Smad7. In CD, there is overexpression of Smad7, which blocks activation of the transforming growth factor β1 (TGFβ1) pathway [72]. TGFβ1 suppresses inflammation in CD. Mongersen has a pH-dependent coating designed to deliver targeted therapy to the terminal ileum and right colon [73].

Clinical Data

Three mongersen doses (10, 40, or 160 mg) have been evaluated in ileo-colonic CD [81]. Clinical remission at the primary end point on day 15 was 55% and 65% for the 40 and 160 mg groups, respectively, compared to just 10% of the placebo group [73]. The 10 mg group performed similarly to the placebo group. At reassessment on day 28, 62% and 67% of patients treated with 40 and 160 mg, respectively, were in clinical remission. Patients were followed out to week 12 with consistent superiority of 40 and 160 mg doses in achieving clinical remission over placebo and 10 mg dosing [74]. Of note, patients with CD proximal to the terminal ileum, strictures, fistulae, and perianal disease were excluded from this trial. Phase III trials are ongoing.

Conclusions

While there are innumerable approaches being investigated evaluating individual components of the IBD *interactome* a more systematic, step-wise approach is needed to combine prognostic markers towards unified molecular phenotypes [1]. Such trials of novel therapeutics and dietary approaches have been recently reviewed [75-82]. Meanwhile, the inclusion of biomarkers into the design of clinical trials is essential to provide better insights into pathophysiology, stratification of treatment, specific bio-marker responses, and better designs of future trials [3]. Additional potential solutions to precision medicine in IBD could include: data-driven approaches such as network interference, prospective studies with multiple time points, standardized methods of bio-sample acquisition, and homogeneous patient subsets and studies of subjects with no prior medical therapy [3]. Algorithmic-based approaches incorporating such aspects and stratification based on clinical, genetic, serologic and multi-omics should be added to clinically based, prognostic factors (e.g. phenotype, disease duration, diet, smoking, etc.) (Figure 4) [83].

Until or unless the pathogenesis of individual UC or CD are clarified (remember *H. pylori* and the prior concepts of peptic ulcer pathogenesis) we will be left with a ***glass half-filled*** approach to personalized approaches IBD therapy in the future.

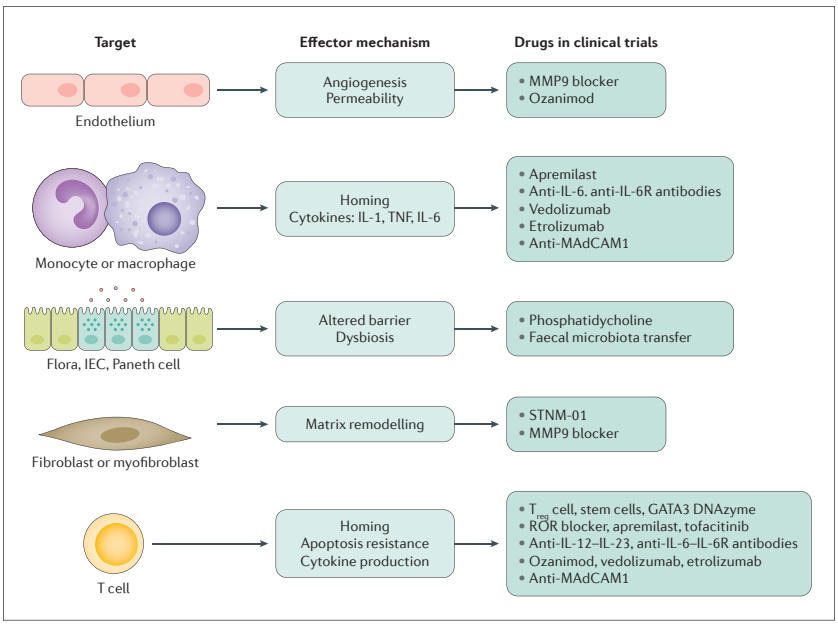

Figure 4: *New therapeutic approaches in IBD with their specific targets (from Neurath [81])*

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CURRENT AND FUTURE
MANAGEMENT OF DIGESTIVE
DISEASE: FROM BENCH TO BEDSIDE

Notes


CURRENT AND FUTURE
MANAGEMENT OF DIGESTIVE
DISEASE: FROM BENCH TO BEDSIDE

Notes

SATURDAY, November 10, 2018 – Morning

SESSION III:
GUT MICROBIOTA

CHAIRED BY:


Peter B. Ernst

Peter B. Ernst, DVM, PhD
Professor, Department of Pathology
Head, Division of Comparative Pathology and Medicine
Co-Director, UC Veterinary Medical Center
University of California, San Diego, CA, USA


CURRENT AND FUTURE
MANAGEMENT OF DIGESTIVE
DISEASE: FROM BENCH TO BEDSIDE

Notes

SATURDAY, November 10, 2018 – Morning

SESSION III: GUT MICROBIOTA

Chairman: Peter B. Ernst, *DVM, PhD (San Diego, CA, USA)*

09:00 Esophageal and Gastric Microbiome in Health and Disease
Richard H. Hunt, *MB ChB, FRCP, FRCPC, AGAF, MACG, MWGO (Hamilton, ON, CA)*

09:30 Alterations of Gut Microbiome: Implications for the Clinician
Eammon M.M. Quigley, *MD, FRCP, FRCPI, FACP, MACG (Houston, TX, USA)*

10:00 Diet and Drug Induced Dysbiosis
Nimish Vakil, *MD, FACP, AGAF, FASGE, FACG (Milwaukee, WI, USA)*

10:30 *Coffee Break*

11:00 Influence of *Helicobacter* Infection and Its Eradication on Gut Microbiota
Colm O'Morain, *MD, Msc, MRCPI, DSc, FRCPI, MRIA, FRCP, FEBGH, FACG (Dublin, Ireland)*

11:30 Microbiota-directed Therapies in Digestive Disease
Focus on Probiotics and Chronic Intestinal Disorders
Mario Guslandi, *MD, FACG (Milan, Italy)*

12:00 Fecal Microbiota Transplantation: Beyond *C. difficile* Infection
David Armstrong, *MA, MB BChir, FRCPC, FRCP(UK), AGAF, FACG (Hamilton, ON, CA)*

12:30 *Closing Remarks*
Carmelo Scarpignato, *MD, DSc, PharmD, FRCP, FACP, FCP, FACG (San Ġiljan, Malta)*

13:00 *Working Lunch*


Richard H. Hunt

09:00 Esophageal and Gastric Microbiome in Health and Disease

Richard H. Hunt, MB ChB, FRCP, FRCPC, AGAF, MACG, MWGO

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Introduction

The microbiota of the upper GI tract is less studied than the lower GI tract, with the exception of *Helicobacter pylori (H. Pylori)* in the stomach. Until recently, most reports have focused on phenomenological observations and associations rather than the underlying physiologic or pathophysiologic mechanisms. The discovery of *H. pylori* by Marshall and Warren in 1982 [1–3] has led to understanding of the unique characteristics of this remarkable bacterium, which colonizes and alters the immunologic and physiologic functions of the host stomach.

H. pylori challenged the view that hydrochloric acid and pepsin ensured a sterile stomach in spite of many reports from the nineteenth and early twentieth centuries describing bacteria in gastric juice [4]. This endorsed the commonly held opinion that *Helicobacter* species are the only organisms able to colonize the human stomach. However, many other organisms occupy the gastric mucosa and lumen and modern microbiological techniques confirm that the microbiota of the stomach involves hundreds of phylotypes with a microbial density of 10^1-10^3 colony-forming units (CFU)/g [5–7]. Anatomical and physiological characteristics of the stomach differentiate the microbiota from that in the oesophagus and elsewhere in the gastrointestinal tract.

The terms microbiome and microbiota comprise the bacterial, fungal, viral, and potentially prion, populations. This review addresses the bacterial components of the oesophagus and stomach and the essential differences that require consideration.

The Microbiome of the Healthy Esophagus

In contrast to the oral cavity, the stomach or colon, under normal conditions the esophagus acts as a channel for food and does not retain any solid contents.

Culture from esophageal washings suggest that bacteria were either swallowed from the oral cavity or refluxed from the stomach [8]. Bacterial flora of the oral cavity and the esophagus, show *Streptococcus viridans* is the most common bacterium [9].

Techniques of bacterial detection, which are independent of culture, characterize the diversity of the esophageal microbiota. In healthy individuals, using broad-range 16S rDNA polymerase chain reaction (PCR) applied to esophageal biopsies, microbial diversity showed the prevalent organisms to be Streptococcus, Prevotella, and Veillonella [10,11]. Using PCR of biopsies from the distal esophagus in healthy volunteers and patients with either esophagitis or Barrett's esophagus (BE) showed Streptococcus dominating in the healthy esophagus, but in contrast, gram-negative anaerobes dominated in both esophagitis and BE [12]. This has led to designation into 2 distinct types: type I and type II, respectively, for the 2 conditions.

The Esophageal Microbiome in Disease

Changes in the microbiota of the lower esophagus have been described in reflux disease, Barrett's esophagus (BE), and esophageal carcinoma, and also in eosinophilic esophagitis in a pediatric population [13-15].

In patients with severe reflux, histologic changes have been described with T-lymphocyte predominant inflammation with papillary and basal cell hyperplasia but no loss of surface cells [16] suggesting inflammation may be cytokine mediated rather than result from acid peptic injury. Furthermore, alterations in the esophageal microbiome with increasing gram-negative bacteria may drive esophageal inflammation in esophagitis and BE [12]. Gram-negative bacteria lipopolysaccharide can upregulate gene expression and proinflammatory cytokine production can also be increased. Gram-negative anaerobes predominate in the presence of inflammation and BE (type II) [14,17,18] the changing nature of the bacteria found in the upper gastrointestinal tract is highlighted by the overlap between the esophageal and gastric microbiome.

Esophageal Cancer

Adenocarcinoma of the distal esophagus and gastroesophageal junction has increased across the western world especially in white males and is causally associated with reflux esophagitis [19].

Infection with *H. pylori* protects from distal esophageal cancer through gastric atrophy and reduced acid secretion and there is altered regulation of cytokine and gastric hormonal control of acid secretion and also with changes in the microbiota [14,20]. In a Chinese study in healthy volunteers and patients, after adjusting for gender, smoking, age, and antibiotic use a significant positive association was seen between microbial richness and pepsinogen I/II ratio and an inverse association with esophageal squamous dysplasia [21]. The findings suggest that with lower microbial diversity chronic atrophic gastritis and esophageal squamous dysplasia are more likely. Correlation showed a significant decrease in esophageal squamous dysplasia with increasing microbial richness.

Gastric Microbiome

Microbes in humans interact with their host and also with each other, which can lead to ***dysbiosis*** [22]. Dysbiosis usually refers to increased levels of potentially harmful or harmful bacteria while conversely, reduced levels of bacteria that are considered to be beneficial. Historically, the stomach has been considered germ-free due to acidity and the digestive nature of gastric juice. Scientific reports from the 19th Century have described finding bacteria in the stomach [4]. A particularly interesting report came from Jaworski (1899), who was studying gastric juice from the human stomach and reported spiral-shaped bacteria and rod-shaped bacilli, which when isolated and cultured produced lactic acid [23]. He confirmed that more than one bacterial species could colonize the stomach simultaneously and speculated that spiral-shaped bacteria might be involved in the pathogenesis of stomach ulcer, stomach cancer, and achylia.

Subsequently in 1982, Marshall and Warren [3] described *Campylobacter pyloridis*, which was renamed *H. pylori* in 1989. Research into *H. pylori* has led to a sea change in our concepts of bacteria and the stomach [5-7]. The survival mechanisms by which *H. pylori* successfully colonizes and replicates within the acidic digestive gastric juice suggest these are unique attributes [24]. pH values <4 largely prevent bacterial overgrowth, but gastric juice is not able to sterilize the stomach [7,25]. *H. pylori* is not the only microbe that can colonize the gastric mucosa and Lactobacillus species are also found colonizing the gastric mucosa [26-28]. *Lactobacillus spp* convert lactose to lactic acid which acidifies the gastric mucous layer overlying the gastric epithelium [29] and explains its adaptation to the stomach. Other species found to survive in the stomach include *Yersinia enterocolitica*, which has an acid-activated urease mechanism, and *Vibrio cholerae*, which shows acid tolerance maintaining the cytoplasm at pH 4-5, although replication does not occur [25,29].

Gastric microbial density is dynamic between 10^2 and 10^4 CFU/g. [6,7,30], but with fluctuations in microbial density, varying with intragastric pH, and in both the quantity and the proportion of genera [31,32]. Gastric juice is largely composed of proteolytic enzymes and hydrochloric acid and this reduces the quantity of microorganisms and especially pathogens which enter the small intestine [33,34]. Human gastric secretion is influenced by meals and has an inter-prandial pH of between pH 1 and 2 in the gastric lumen, but this rises to pH 5.5 with ingestion of food. The pH also varies within the stomach from the most acidic fundus containing the parietal cells and the less acidic antrum. There is also a pH gradient from the gastric juice in the lumen with pH 1-2 to the surface of the gastric epithelium where pH approximates 7. The mucus layer consists of an inner mucus layer, firmly attached to epithelial cells and a variable mucus layer interfacing with the lumen [33-36,37].

To better understand the dynamics, it is necessary to consider the site of bacterial sampling. When isolated from gastric juice, bacteria and bacterial DNA are different

from isolates adherent to gastric mucosa, which is a more hospitable environment for colonization within the buffered mucus layer. When acid secretion is reduced or inhibited the risk of bacterial overgrowth increases and this influences the composition of intestinal or oral microorganisms, including pathogens [32] and nitrate reducing bacteria which can nitrosate dietary nitrate and nitrite and are not commonly cultured from a healthy stomach [38].

Helicobacter pylori

H. pylori infection is the dominant gastric organism in *H. pylori*-positive patients when detected by conventional methods [39-42]. *H. pylori* is able to survive in the low pH of the stomach by producing urease and ammonia [24,43,46]. Alkalinization of its microenvironment enables survival within the fluctuating acidity of gastric juice and protects the organism until it reaches the higher pH of the mucous layer where it can colonize in close apposition to the epithelial cell surface. The acute inflammatory response to *H. pylori* infection results in IL-8 release and recruitment of inflammatory cells leading to chronic active gastritis [45,46]. The immunology of the stomach and host response involved in the persistence of *H. pylori* infection and the role of other organisms are an important new focus for current research into the gastric microbiome [5].

Gastric Microbiota in Healthy Individuals

Soon after the discovery of *H. pylori*, Veillonella, Lactobacillus and Clostridium were also reported in the human stomach [47]. The gastric microbiota differs from that in the oro-pharynx [30] and suggests that the stomach has a resident population of bacteria other than those ingested from the oropharynx or esophagus.

The finding of non-*H. pylori* bacteria in human gastric mucosa has been confirmed by conventional histology [48] and culture of both gastric juice and mucosal biopsies [49-51]. Based on culture in the healthy human stomach, Clostridium spp, Lactobacillus spp, and Veillonella spp are the most reported [47]. The majority of gastric bacteria are not easy to culture,52 but molecular techniques based on 16S rRNA are finding several other genera, including Neisseria, Haemophilus, Prevotella, Streptococcus, and Porphyromonas [30,40,53,54]. In health, the most common bacteria are Actinobacteria (Rothia, Actinomyces, and Micrococcus), Bacteroidetes (Prevotella species), Firmicutes (Streptococcus and Bacillus), and Proteobacteria (which include *H. pylori* as well as Haemophilus, Actinobacillus, and Neisseria), and the predominant genus is Streptococcus, which may come from the oral or nasal cavities [40,54–56].

Variability in the gastric microbiota occurs with geographic and cultural differences, and also differing methodologies. The gastric microbiota in patients infected with *H. pylori* generally differs from uninfected people [56,57] who show a greater diversity than *H. pylori*-positive patients [56] although a Malaysian study suggests this is not a universal finding [58].

H. pylori growth *in vitro* was inhibited by *Lactobacillus johnsonii, Lactobacillus murinus,* and *Lactobacillus reuteri* [59] and some Lactobacillus, Bifidobacteria, and Saccharomyces prevented adhesion and colonization of *H. pylori* [59]. In another study, 2 *Lactobacillus reuteri* strains, isolated from gastric juice and biopsies, showed resistance to acid and a strong antimicrobial effect against *H. pylori* [60]. The mechanisms of altering the gastric microbiota by *H. pylori* or other bacteria is still unclear but direct killing of bacteria by the induction of host antimicrobial peptides, such as ß-defensin 2 [61] or cecropin-like peptide have been suggested [62]. *H. pylori* infection initiates an inflammatory response which may result in reduced acid secretion from parietal cells with consequent rise in intragastric pH, which subsequently results in gastric colonization by other microorganisms [63–66], which may predispose to gastric cancer [67].

Interaction between *H. pylori* and Other Microbiota

In the absence of *H. pylori* infection, the structure and composition of the gastric microbiota resembles that of the distal esophagus [56,68]. However, the effects of *H. pylori* infection on the gastric microbiota are not fully understood. *H. pylori* density increases with the onset of gastritis [69], which may allow *H. pylori* to outcompete other bacteria [40]. In one study, *H. pylori* accounted for 93% to 97% of all reads in the infected stomach with substantially decreased diversity – only 33 phylotypes were observed in *H. pylori*-positive patients compared with 262 in *H. pylori*–negative subjects [56].

H. pylori infection and its associated gastric effects alter the ecological niche of the gastric microbiota. However, the gastric microbiota also competes with *H. pylori* and may be important in disease progression.

Interpreting Esophageal and Gastric Microbiota		
•	Esophagus / stomach host their own bacterial populations	
•	Microbiota differ in health from disease	
•	*H. pylori:*	Colonize **only** gastric epithelium
		Alters other bacterial populations
		Reduces diversity
•	Bacteria influenced by:	Acidity / secretion
		Site of isolation
•	Bacteria may be:	Swallowed from the oro-pharynx
		Transient or colonizing
Studies (to date other than *Hp*) provide associations but **NOT** evidence of causality		

Lactobacillus

Lactobacillus species are found in the stomachs of all mammals, and several studies report Lactobacillus colonizing the human gastric mucosa [30,50,51,70–73]. Lactobacilli are rod-shaped, gram-positive, micro-aerophilic bacteria with some similarities to *H. pylori.* Lactobacilli convert lactose to lactic acid, leading to acidification of the bacterial microenvironment, and consequently acidification of the gastric mucous layer [27]. With these acidophilic properties, Lactobacilli adapt sufficiently to colonize the stomach [28,29] and some Lactobacilli have a urease enzyme which is similar to that of *H. pylori* [74,75].

Acidification of the gastric antral mucosa causes rapid inhibition of gastrin and a fall in gastric acid secretion [76–78]. Consequently, acid-generating Lactobacilli close to the surface of the antral gastric epithelium can inhibit gastrin release and so decrease gastric acid secretion (Figure 1). In contrast, *H. pylori* alkalinizes the gastric antral mucosa through urease activity, increasing gastrin and acid secretion [79]. Lactic acid produced by Lactobacilli neutralizes ammonia produced by *H. pylori*, resulting in a null net effect on pH at gastric epithelial surface when both *H. pylori* and Lactobacilli co-colonize the stomach (Figure 1) [79].

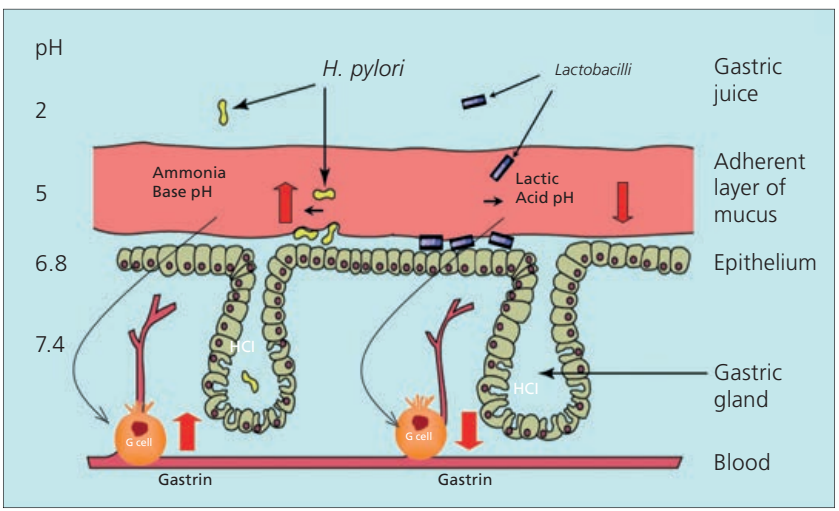

Figure 1: *Lactobacilli and* H. pylori *can both modulate gastric acid secretion. Lactobacilli metabolism produces lactic acid (0.25 M-0.50 M), which can acidify mucus in the gastric antrum and thus lower gastrin. In contrast,* H. pylori *urease produces ammonia which alkalinizes antral mucus thus raising gastrin secretion (adapted from Padol & Hunt [79])*

In *H. pylori*-infected patients a probiotic, which included *Lactobacillus rhamnosus,* significantly decreased serum gastrin-17 [80]. Some Lactobacilli inhibit *H. pylori* [81,82] and probiotics isolated from dairy products or human feces have been shown to suppress *H. pylori.* In culture, Lactobacilli producing lactic acid (0.25 M-0.50 M) also modulate *H. pylori* bacteria at this concentration (George Sachs, *personal communication*, 2009).

In a single-blinded, randomized, placebo-controlled pilot study, *L. reuteri* DSM17648 co-aggregated the pathogen *in vitro* and *in vivo* and significantly reduced *H. pylori* load in healthy, yet infected adults [83]. Interestingly, a new strain of *L. johnsonii* No. 1088 has shown the best acid resistance among several Lactobacilli studied with >10% of organisms surviving at pH of 1 after 2 hours. *L. johnsonii* also inhibited *H. pylori* growth, *Escherichia coli* O-157, *Salmonella typhimurium*, and *Clostridium difficile* in vitro and suppressed gastric acid secretion in mice [84].

Gastric Microbiota in Disease

Gastric Cancer

H. pylori is the most important microbial risk factor and a class I carcinogen for the development of gastric cancer [85]. Other gastric microbiota are implicated in the carcinogenic pathway through inflammation, an increase in cell proliferation, dysregulation of stem cell physiology and production of several metabolites [86].16S rRNA gene sequencing analysis of the gastric mucosa of gastric cancer patients show a higher prevalence of *Lactobacillus, Streptococcus mitis, Streptococcus parasanguinis*, Prevotella, and Veillonella [42]. Another study, using a high-throughput sequencing platform (454 GS FLX Titanium) showed greater bacterial diversity, a relative increase of Bacilli and *Streptoccocci spp*, and a relative reduction of Helicobacteraceae in the cancer group compared with other groups [41]. Although results lack consistency, this may reflect a change in gastric microbiota across the stepwise progression to gastric cancer.

H. pylori infection markedly alters the structure of microbial communities, but the relative proportions of the other members of the microbiota are not markedly changed. Gastric cancer patients show an enriched population of 5 genera of bacteria, all known cancer promoting potential, including Lactobacillus, Escherichia, Shigella, Nitrospirae, Burkholderia fungorum, and Lachnospiraceae. Nitrospirae was present in all patients with gastric cancer, but not found in patients with chronic gastritis [87].

Interpreting bacterial diversity in gastric cancer is confounded by bacterial overgrowth in the stomach which has also been reported in precancerous conditions [30,88], including hypochlorhydria and gastric mucosal atrophy. It is not clear if bacterial overgrowth is a consequence of the carcinogenic process creating an environment favoring bacterial proliferation.

Atrophic Gastritis

Gastric acidity and peptic activity provide a barrier to bacteria in food and saliva [89,90]. Any decline of gastric acid secretion with age is essentially due to chronic atrophic gastritis rather than age per-se and can lead to microbial colonization of the stomach. Data on gastric microbiota composition in patients with chronic atrophic gastritis are too limited to comment on the overall changes so far reported.

Functional Dyspepsia

A Japanese study reported changes in gastric microbiota and bile acids were greater in the gastric juice of patients with functional dyspepsia (FD) than healthy controls. Bacteroidetes exceeded Proteobacteria with an absence of Acidobacteria in the FD group compared with the healthy controls, who in contrast had a Bacteroidetes abundance exceeding Proteobacteria and with Acidobacteria present. Probiotic treatment shifted the microbiota composition of the gastric juice to that seen in healthy volunteers [91].

FD may follow an infection and currently recognized as post-infectious FD (PIFD) [92,93]. One report found 17% of FD patients had experienced an episode of acute gastroenteritis and the onset did not correlate with *H. pylori* infection [94]. The incidence of FD was significantly higher in patients 1 year after acute Salmonella gastroenteritis in one prospective study (13.4%) when compared with controls (2%) [95]. A meta-analysis reported mean FD prevalence FD after gastroenteritis was 9.55% in an adult population with an OR for post infective FD was 2.54 (95% CI: 1.76-0.65) [96]. The mechanisms involved in post-infective FD is not well understood but the altered immune response to dysbiosis in the upper GI tract seems involved. Whether gastroenteritis changes the gastric microbiota or only influences the occurrence of dyspepsia is not yet known.

The apparent success of a probiotic intervention in FD [91] should be considered carefully in view of two recent reports, which highlight that probiotics have differing effects between individuals and along the extent of the GI tract and may impede the return of the microbiome to pre-treatment baseline after interventions, including antibiotics or fecal microbiota transplant [97,98]. The clinical significance of these observations are unclear at this time, but make clear the need for further study.

Rifaximin is a poorly absorbed antibiotic used in IBS and hepatic encephalopathy and postulated to influence the gut microbiota. It has improved symptoms of pain and bloating in IBS and these are also important symptoms in FD. Moreover, duodenal bacterial load is directly correlated with symptom severity in FD [99], suggesting a possible role of poorly absorbed antibiotics in functional dyspepsia. A double-blinded, randomized, placebo-controlled trial of rifaximin for symptoms of FD has been reported in Chinese patients [100]. At week 8, significantly more patients on rifaximin

experienced adequate relief of global dyspepsia symptoms of belching and post-prandial fullness/bloating (78% *versus* 52%, P = 0.02) than in the placebo group. The difference was more marked in females.

Effect of Acid Suppression on the Gastric Microbiome

There is a logarithmic relationship between intragastric pH and median bacterial counts in gastric juice (Figure 2), so that rising pH increases the risks for bacterial associated diarrhea and enteric infections [48,101].

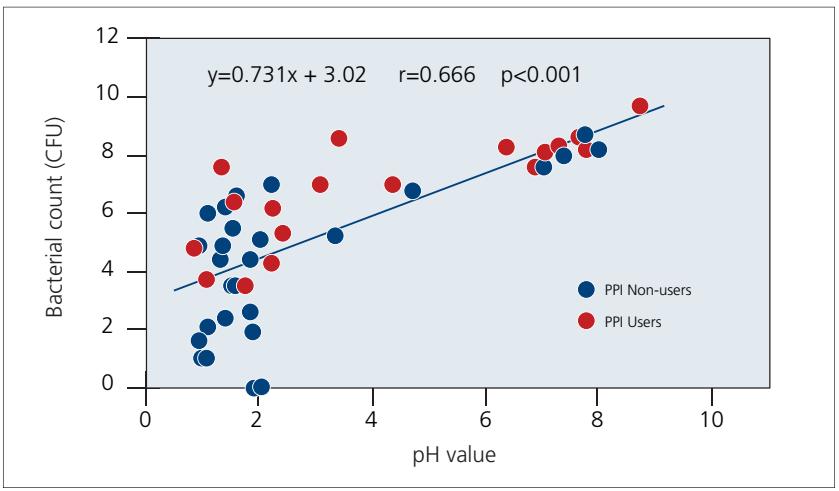

Figure 2: *The effect of intragastric pH on bacterial counts determined by culture of gastric juice is shown with bacterial count on the vertical axis and pH on the horizontal axis for each subject and according to PPI users and non-users.* (modified from *Tsuda* et al. *[108])*

Concerns over therapeutic acid suppression, with H_2RAs and PPIs has focused on nitrate reducing bacteria in the stomach [102-104]. In a 2-week study with cimetidine, intragastric acidity, intragastric bacteria, nitrite, and N-nitroso compounds were evaluated before, during, and after treatment [32]. No significant differences were found in bacterial counts or bacterial species between the 3 time periods. Bacterial counts and nitrite concentrations tended to increase with pH, but N-nitroso compounds did not. As pH became more acidic, bacterial counts decreased. PPIs elevate intragastric pH levels to a greater degree than H2Ras [105] and in a similar study before, during, and after omeprazole [106] a short-lived increase in the bacterial flora with a profile similar

to that reported with cimetidine and similar effect on endogenous N-nitroso compounds was found [32,106]. The role of ingested dietary nitrite and nitrate and the risk of gastric cancer has been recently reviewed leading to a paradigm change in the concerns of both nitrite and nitrate [107], which are now thought to be indispensable for cardiovascular health. In the absence of a co-administered carcinogenic nitrosamine precursor, there is no evidence to support carcinogenesis. Moreover, prospective epidemiology cohort studies show no association between the estimated dietary nitrate or nitrite intake and gastric cancer [107].

In a study comparing PPI users with PPI non-users, bacterial numbers increased ~1000 fold in gastric juice of PPI users (measured by culture methods). However, bacterial numbers and composition were almost identical between PPI users and non-users (measured by quantitative PCR and a similarity search using 16S profiling). The authors concluded that microbiota in gastric juice had migrated from saliva and that bacterial overgrowth might result from acid suppression leading to a lack of bacterial killing rather than bacterial proliferation [108].

Several reviews of the adverse effects of acid suppression [105,109,110] confirm modest increases in the risk of enteric infection particularly with Salmonella, Campylobacter, and Shigella. There is also a significant risk of *C. difficile* in a meta-analysis of 39 studies [111].

Epidemic or spontaneous hypochlorhydria is well documented [112-115] and case reports and reviews of the literature suggest that most were associated with *H. pylori* infection for which two group studies [112,113] and a report by Graham [114] provide some supportive evidence. The mechanisms involved, are unclear, although isolated parietal cell studies have shown acid secretory inhibition by *Campylobacter pylori* (as it was then known) organisms [116] and by a protein extracted from that organism [117].

Conclusions

New concepts and rapidly evolving research technologies are improving our understanding of the complex nature of the esophageal and gastric microbiome. To date many studies have been small and presented phenomenological observations and clinical associations rather than prospective research into immune or patho-physiologic mechanisms. Confusion also stems from the interpretation of animal and human studies. Furthermore, reports often relate to changes in the gastrointestinal microbiota by focusing on changes in fecal microbiota rather than the esophageal or gastric microbiota, even when PPIs are studied.

It is probably naive to suppose that other single bacteria with selective pathogenicity will be found, such as with *H. pylori* infection, where research has revealed the complexity of this bacterium and our host response to it. There is, so far, no evidence for adherence or cellular invasion from any other bacteria in the stomach (or esophagus).

However, it seems increasingly clear that disease may result from dysbiosis not requiring adherence or invasion as a prerequisite for pathogenesis.

More studies involving the microbiota-host-environment interactions, including the effect of diet, geography, culture, and gender, are awaited to fully understand the role of the gastric microbiota in health and disease.

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Eammon M.M. Quigley

09:30 Alterations in the Gut Microbiome: Implications for the Clinician

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Background

We are in the midst of what, rightly or wrongly, has been termed "the microbiome revolution" [1] – not a day goes by without some new revelation on the biology of the gut microbiome, or yet another claim for a fundamental role for gut commensals in the pathogenesis of some disease state. Over recent decades, basic science research has revealed, not only the intimacy and complexity of mutually beneficial interactions between gut microbiota, the epithelium and the gut barrier [2,3] as well as the mucosal immune system [4,5], but also interplay between luminal commensals and the enteric nervous system and gut muscle [6-9]. That the microbiota might play role in such gastrointestinal disorders as celiac disease [3], inflammatory bowel disease [2] and functional and motility disorders [10, 11] should come as no surprise, therefore. Indeed, through effects on neuroendocrine [7], immune [4] and metabolic functions [12], a role for the microbiota in disorders as diverse as arthritis [13] and liver disease [12] has been proposed. The recent suggestion that interactions between microbiota and gut could extend all the way to the central nervous system via what is referred to as the microbiota-gut-brain axis [14] now provides a framework for the incrimination of gut bacteria in neurological disorders such as Parkinson's disease [15].

Microbiome and Gastrointestinal Disease – Advances in Pathogenesis

Experiments involving a variety of *in vitro, in vivo* and *ex vivo* models have explored the role of the microbiome in the pathophysiology of gut disease and the pathogenesis of gut-derived symptoms [16-20]. At a fundamental level many of these disorders seem to involve variable interactions between ***a normal or disturbed microbiome, microbial metabolic products, the host genome*** (regulating such factors as the immune response), ***the gut barrier*** (in its broadest sense), ***the host immune response, host physiology*** and not forgetting ***interactions with dietary and other micro- and macro-environmental factors*** (Figure 1). Given that many of these interactions are bidirectional one can readily appreciate the challenge the investigator faces in attempting to isolate the role of the microbiome in a given disease state (Figure 2).

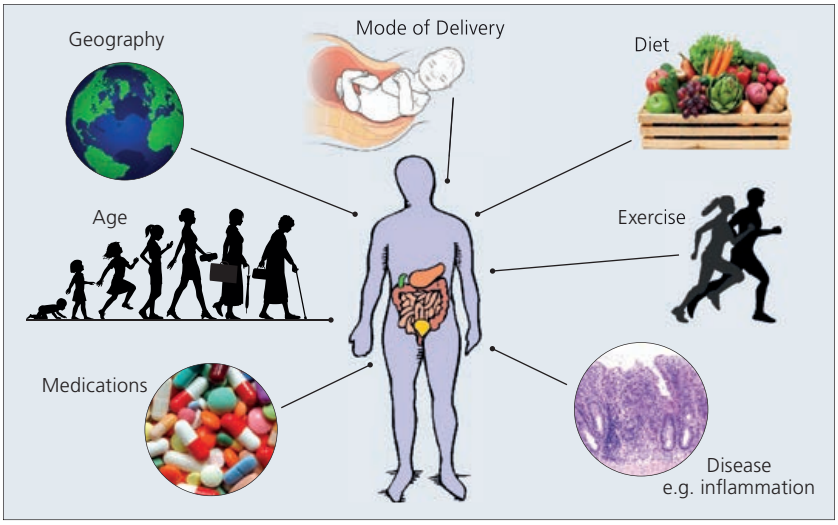

Figure 1: *Some of the factors that influence the composition of the gut microbiome*

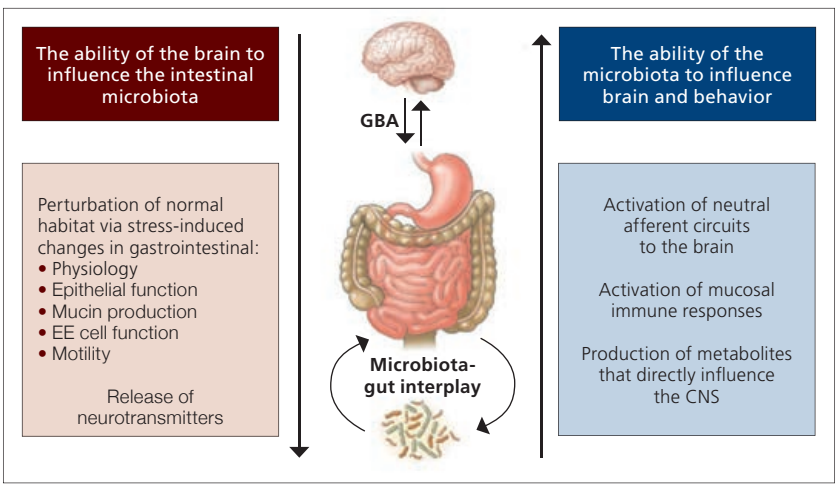

Figure 2: *Microbiota-gut-brain axis is bidirectional*

Some progress has been made. The impact of a gross disturbance of the microbiome is most readily appreciated in the context of enteric infections and the protective role of an intact commensal bacterial community vividly illustrated by the development of *Clostridium difficile* infection when the former is suppressed by antibiotic therapy [21]. A microbial signature that predisposes the individual to this potentially life-threatening infection has been described [22,23] and fecal microbial transplantation (FMT) has been shown to restore resistance to *C. difficile* [24].

Interactions between bacterial pathogenicity, the host genome and, in turn, the host immune response have been shown to play a central and interlinked role in determining the disease phenotype that emerges from infection with *Helicobacter pylori* [25-28]. Though the resultant phenotype is more heterogeneous, a convergence of bacterial and host immune responses is also suggested as being central to the pathogenesis of inflammatory bowel disease (IBD), as illustrated by the prevalence of polymorphisms in genes involved in the host response to bacteria among the multitude of genes that have been linked to both Crohn's disease and ulcerative colitis [29].

In an overly simplistic concept, impaired gut barrier function has been frequently incriminated in the pathogenesis of microbiota-induced (or -related) gastrointestinal and systemic disorders. According to this model, a "leaky gut" permits the translocation of bacteria or bacterial products, such as lipopolysaccharide, from Gram-negative bacteria, across the damaged epithelium where it ultimately accesses the portal or even systemic circulations (Figure 3) [30]. There are several problems with this hypothesis, attractive though it may be. Firstly, measures of translocation have proven unreliable and variably reproducible in man, in contrast to animal models [31]. Secondly, tests of intestinal permeability in man typically involve methodologies that assess the integrity of the para-cellular pathway, a pathway involved in the passage of ions and water and scarcely able to transport the large molecules that are bacterial products, not to mind whole bacteria [32]. This is not to say that the detection of para-cellular leakiness may not serve as an indirect indicator of an insult to the epithelium that may also injure trans-cellular and other pathways that could result in the translocation of bacteria and/or their products. Finally, other components of gut defense, such as a gut-vascular barrier may be central to the systemic dissemination of enteric bacteria [33,34].

Certain bacterial metabolic products are seen to play critical roles in the pathogenesis of symptoms and even in the etiology of gut and systemic diseases. Bile acids enjoy a complex and bidirectional relationship with the microbiome. On the one hand, bile acids exert bacteriostatic effects which certain bacterial species learn to evade through the possession of the enzyme bile salt hydrolase [35]; on the other hand, bacterial metabolism of primary bile acids produces products that may exert, through their ever-expanding repertoire of regulatory functions, effects on host metabolism and immune responses [36-38], as well as on colonic motility and secretion.

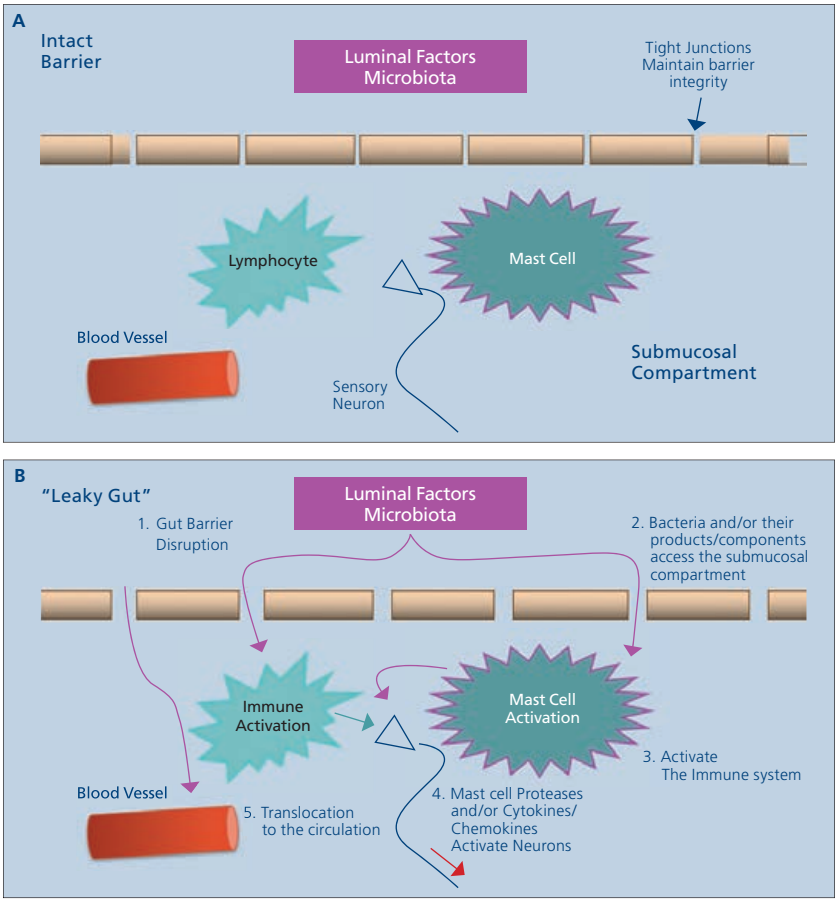

Figure 3: *Interactions between the microbiota, the gut barrier, the mucosal immune stem and gut function in* A) *health and* B) *impaired barrier function*

Short chain fatty acids (SCFA's) are an important product of bacterial metabolism of undigested carbohydrates. Long recognized as critical fuels for the colonic epithelium, other effects of SCFA's, such as immune modulation and neuro-endocrine signaling are increasingly recognized [39,40].

From Mouse to Man – Lost in Translation?

It should be evident from the aforementioned overview of pathogenetic and pathophysiologic factors related to the gut microbiome that a multitude of often interacting factors may be at play in a given gastrointestinal disease [41-44] and that the definition of their relative importance, while feasible in animal models, may prove very challenging or even elusive in man. Defining what is there using high-throughput sequencing may be a good first step but will merely document association and certainly not prove causation [45]. A more complete delineation of a pathogenetic role of a given microbial signature may be intimated from metagenomics [45] and supported by metabolomics. Longitudinal studies with sampling at multiple time points (a rarity in human studies) which track for disease activity and/or symptom intensity will also assist in differentiating signals that are state from those that are trait. Ultimately, a symptomatic response or cure consequent upon an intervention directed at the microbiome should clinch its role in a given disorder; though recent work on hepatic encephalopathy (HE; perhaps the original microbiome-gut axis disorder) illustrates the complexity of interpreting such responses. In an investigation of the pathogenesis of the beneficial impact of the poorly absorbed antibiotic rifaximin in HE, it was found that the amelioration of encephalopathy in response to treatment with this antibiotic owed more to shifts in bacterial metabolism rather than changes in the composition of the microbiota [46].

Other challenges confront the clinical researcher. The impact of interactions with components of the diet and its metabolic products, already emphasized above, must be remembered [41,42,47] in translational as well as a clinical research [48]. For example, the multiplicity of diets employed by IBS sufferers which may range from high fiber, to gluten-free and low fermentable oligosaccharide, disaccharide, monosaccharide and polyol (FODMAP) diets, each of which impacts on the microbiome [49,50-52], should be accounted for in studies of the microbiome in this disorder.

Sampling presents its own hurdles. For obvious reasons of convenience, most human studies of the gut microbiome have been based on the analysis of fecal samples. This approach ignores the tremendous variations in bacterial density and populations along the length of the gastrointestinal tract; a microbiome-based disease which primarily involves the small intestine is unlikely to be reflected in a fecal sample. Furthermore, it is also clear that, at any point along the gut, differences are also evident between bacterial populations resident in the lumen and those adherent to the mucosal surface [53]. These mucosa-associated bacterial species and strains will not be accurately represented in fecal samples; a major limitation of this approach. It stands to reason that bacterial species resident at the mucosal surface, or within the mucus layer, are those most likely to participate in interactions with the host immune system and the gut barrier [54] whereas those that populate the lumen may be more relevant to metabolic interactions with food or the products of digestion. Evidence for clear differences between these populations in both health [55] and disease states already exists [56-59].

Timing may also be critical; there is accumulating evidence that disruption of the microbiota in early infancy may be a critical determinant of the expression of certain diseases in later life (Figure 4) [1,60,61]. It follows that diagnostic or therapeutic interventions based on the microbiota and directed at these same disorders later in life may, quite literally, be too late and doomed to failure.

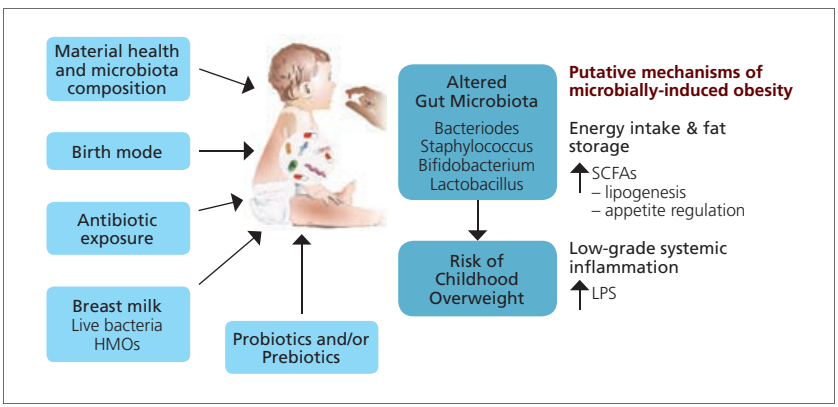

Figure 4: *Pre- and post-natal factors that can modify the infant gut microbiota and their impact on the risk of childhood obesity (form Koleva* et al. *[61])*

Conclusions

The microbiome revolution is certainly upon us [1] and our basic science colleagues have thrown down the gauntlet through their elegant description of the complex and extensive roles of the microbiome in homeostasis, as well as in the pathophysiology of disease in animal models. Meanwhile, the availability of high-throughput sequencing techniques has spawned a profusion of studies of the microbiome in almost every known gastrointestinal, liver and pancreatico-biliary disease. Results, to date have been, at best, confusing and, at worst, conflicting but this has not restrained an unwarranted haste to incriminate "abnormal" bacterial signatures in many of these diseases. However, a clear picture of the role of the microbiome in common gastrointestinal diseases has yet to emerge and has been hampered by a failure to account for confounding factors or to optimize sampling methods. Two recent population-based studies make for sobering reading – in both, diet, stool consistency and medications and not disease were the major contributors to inter-individual variations in the gut microbiome [62,63]. Aware of these limitations and armed with an armamentarium of diverse microbiological tools we are now in a position to perform appropriately powered, longitudinal studies of well-phenotyped populations which have real potential to uncover the role(s) of our bacterial fellow travelers in gastrointestinal disorders.

Such studies are a necessary prelude to the development of novel diagnostic and therapeutic interventions. Until they have been completed, we cannot and should not offer microbiome analysis as a diagnostic or prognostic tool in routine clinical practice.

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Nimish Vakil

10:00 Diet and Drug Induced Dysbiosis

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Introduction

The gut microbiota has a fundamental role in maintaining homeostasis in humans. The gut microbiota refers to the complete population of organisms including bacteria, fungi, viruses, archea and protozoa. In the healthy gastrointestinal tract, the predominant phyla are Firmicutes, Bacteroidetes, Actinobacteria and Verrucomicrobia.

Gut microbes aid in the absorption of nutrients by fermenting carbohydrates and creating butyrate, a short chain fatty acid that is important for the health of colonocytes. Gut microbes may have the ability to metabolize drugs such as digoxin. The gut microbiota can help metabolize environmental contaminants and participate in communications of cells and organs.

Diet Related Changes in the Microbiota and Health

Diet has been shown to have a significant effect on the microbiota and these changes may influence disease incidence. Figure 1 shows the proposed effects of diet in the altered microbiota and its effect on biologic effects and disease in the host [1].

Protein

High protein diets are associated with overall microbial diversity. Pea protein has been shown to increase intestinal short-chain fatty acid levels, which are anti-inflammatory and also contribute to the integrity of the epithelium [2,3].

Fats

The typical Western diet is both high in saturated and trans fats and low in mono and polyunsaturated fats predisposing consumers to a number of diseases including heart disease, inflammatory diseases and colon cancer [4-6].

Carbohydrates

Carbohydrates may be digestible or non-digestible. Digestible carbohydrates are broken down in the small intestine and release glucose into portal vein. These sugars consist of glucose, fructose, sucrose, lactose and starches. Humans consuming high concentrations of these carbohydrates have increased abundance of Bifidobacteria

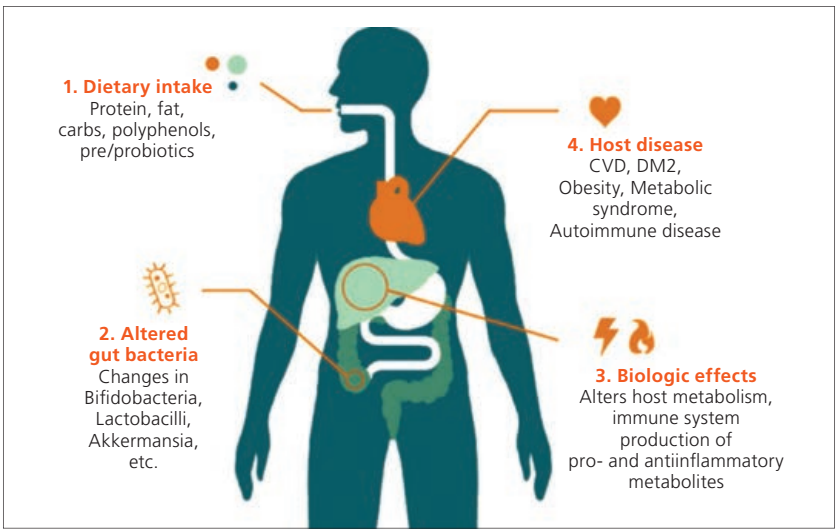


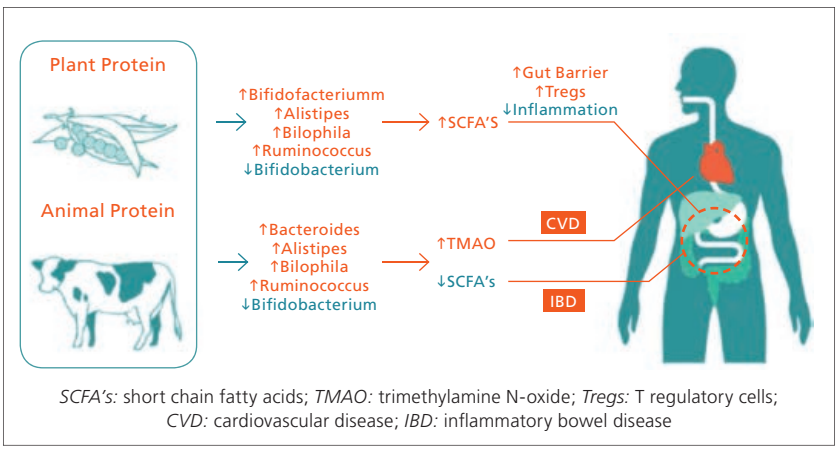
Figure 1: *Impact of diet on the gut microbiome and human health (from Singh* et al. *[1])*

and reduced Bacteroides. Artificial sweetners also alter the microbiome and increase glucose intolerance [7].

Non-digestable Carbohydrates
Fiber and starch are not digested by humans and travel to the colon, where they undergo fermentation producing microbiota accessible carbohydrates (MACs) that colonic bacteria can use to produce energy for the host.

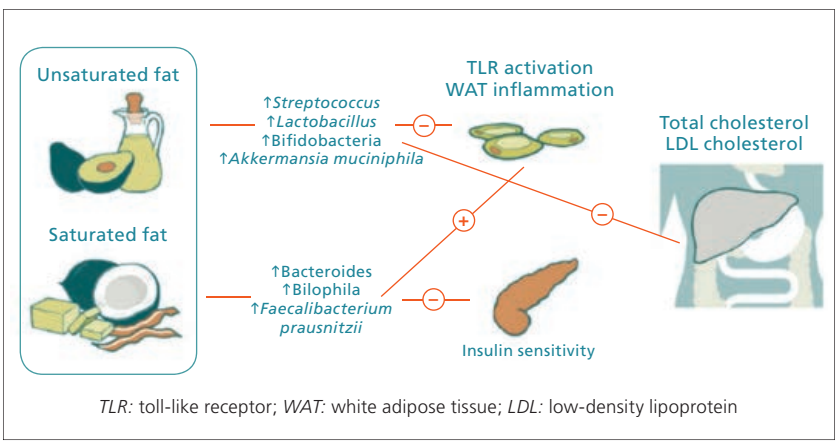
Probiotics
Fermented foods contain micro-organisms benefit the microbiome and treat inflammation.

A plant-based diet (Figure 2) has a significant effect on the microbiota and there are significant differences with populations where animal proteins predominate [1]. Differences in the microbiota may account for differences in disease prevalence. For example, diets high in saturated fat (Figure 3) are associated with increased concentrations of Bacteroides, Biophila and *Fecalbacterium prausnitzii* species [1,8]. The change is associate with activation of Toll-like receptors (TLR) and increased inflammation in white adipose tissue.



SCFA's: short chain fatty acids; *TMAO:* trimethylamine N-oxide; *Tregs:* T regulatory cells; *CVD:* cardiovascular disease; *IBD:* inflammatory bowel disease

Figure 2: *Impact of dietary protein on intestinal microbiota and health outcomes (from Singh* et al. *[1])*



TLR: toll-like receptor; *WAT:* white adipose tissue; *LDL:* low-density lipoprotein

Figure 3: *Impact of dietary fats on intestinal microbiota and host metabolism (from Singh* et al. *[1])*

Disease Associations Between Diet and the Microbiome

Obesity

Obesity is associated with dysbiosis. Obesity has been associated with a decrease in microbial diversity and a change in the phyla Firmicutes and Bacteroidetes [9]. Surgical bypass procedures shift dysbiosis towards a healthy microbiome. Transfer of microbiota from lean individuals to obese individuals increases microbial diversity in the host, improves peripheral insulin sensitivity and increases colonic butyrate levels, expanding the healthy microbiome [10].

Inflammatory Bowel Disease

Patients with inflammatory bowel disease have less bacterial diversity as well as lower numbers of Bacteriodes and Firmicutes. This change in the microbiome may contribute to decreased concentrations of butyrate, which is important for colonic health and has anti-inflammatory effects [11].

Irritable Bowel Syndrome

Dietary therapy has become an important aspect of treatment in irritable bowel syndrome (IBS) [12]. FODMAP is an acronym for fermentable oligosaccharides, disaccharides, monosaccharaides and polyols. IBS is a common medical condition that is associated with abdominal pain, bloating distention, and changes in bowel habit. No single curative treatment exists, and patients often report an association of symptoms with certain foods. In short-term studies (4–6 weeks) of FODMAP restriction in IBS[13,14], 50–80% report an improvement of their symptoms on a low FODMAP diet. A recent meta-analysis evaluated 6 randomized controlled trials and 16 non-randomized trials and reported substantial improvements in abdominal pain, bloating, and overall symptoms with odds ratios ranging from 1.75–1.81 (Figure 4) [15].

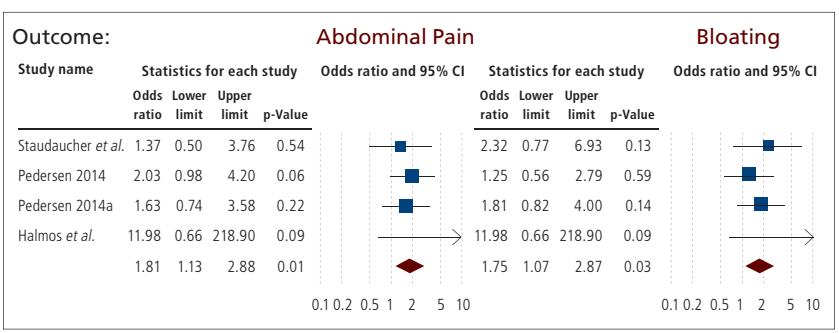


Figure 4: *Efficacy of low FODMAP diet in patients with IBS: a meta-analysis (from Marsh* et al. *[15])*

The FODMAP diet can alter the microbiome decreasing concentrations of Bifidobacteria [14]. Low FODMAP diets are associated with a decrease in liposaccharides (a complex of fat and polysaccharides) in the luminal content of the colon. Intracolonic administration of fecal supernatant from patients with IBS induces visceral hypersensitivity in rats [16]. Administration of a lipopolysaccharide antagonist blocked the increase and fecal supernatant from healthy individuals, and patients with IBS on a low FODMAP diet did not have an effect on visceral hypersensitivity. Low FODMAP diets may therefore alter visceral sensitivity by changing the composition of luminal contents (decreasing luminal short-chain fatty acids and liposaccharides). Short-chain fatty acids have a beneficial effect on epithelial function, and therefore concerns remain about the prolonged use of low FODMAP diets on colonic health and the risk of colon cancer [12].

Drug Induced Alterations in the Microbiome

There are many mechanisms for the detrimental effects of antibiotics on the microbiome (Figure 5) [17].

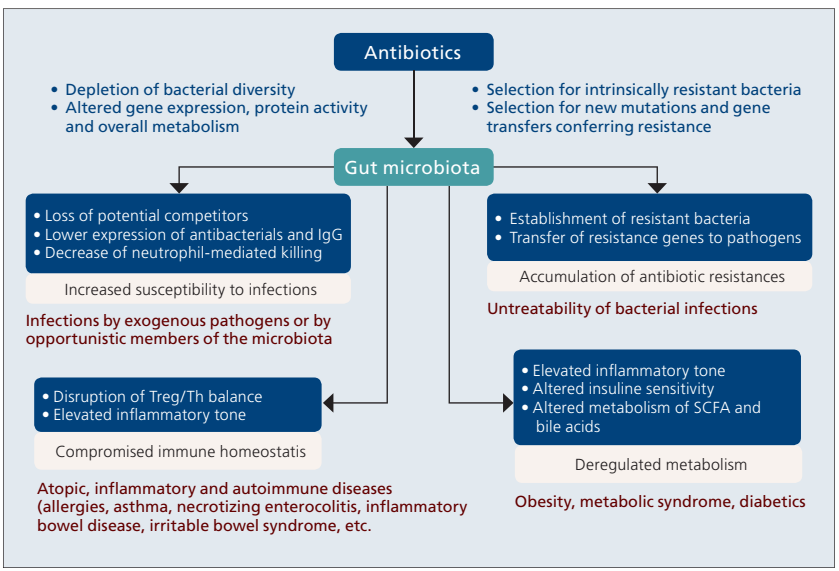


Figure 5: *Antibiotic effects on the gut microbiota and associated health problems. The main biological consequences of antibiotic-induced dysbioses and the potential diseases that can ensue from them are shown (only diseases with published evidence of association with antibiotic exposure are included). Involved mechanisms are shown in red-shaded boxes (from Francino [17])*

Antibiotics disrupt the microbe-microbe and microbe-host interactions that are responsible for hemostasis. Pathogenic organisms normally suppressed by the healthy microbiota can expand with antibiotic use and the pathogenic organisms can compete with the healthy microbiota. Antibiotics can promote the development of resistance and also promote expansion or pre-existing resistant strains. Human studies have evaluated patients after treatment with commonly used antibiotics. Infants given antibiotics may have a higher incidence of atopy and allergies due to alterations in the microbiota [18]. Panda *et al.* demonstrated that fluroquinolones and ß-lactams reduced the core organisms of the microbiota [19]. Clindamycin has a pronounced effect on the microbiota reducing the resistance to colonization with *Clostridium difficile* [20].

Non-antibiotic Drug Effects on the Microbiome

The changes induced by drugs on the microbiome are summarized in Figure 6 [21]. The principal effects that are of importance to clinicians are:

Proton Pump Inhibitors

Several studies have shown a decrease in the diversity of the microbiome of proton pump inhibitor (PPI) users [22-24]. PPIs have been associated with *C. difficile* infections, an increase in enteric infections and an increase in the incidence of *C. difficile* infections in susceptible patients [25-27].

Non-steroidal Anti-inflammatory Drugs

Long terms use of non-steroidal anti-inflammatory drugs (NSAIDs) may lead to hyper-permeation of small intestinal mucosa, and NSAID-induced inhibition of prostaglandin synthesis may lead to decreased blood flow. As a result, the function of the small intestine may be compromised and that could affect the gut microbiota. The type of medication had a greater influence on the gut microbiome than the number of medications. NSAIDs were particularly associated with distinct microbial populations However, changes in bacterial composition of the gut microbiome also depend on the type of ingested NSAID (COX-2 selective or not, acidic or non acidic), suggesting particular mechanisms specific to NSAID class [28].

Opiates

Opioid use is associated with severe constipation, which could be implicated in the creation of a disrupted gut environment leading to altered gut microbiota in the form of small bowel overgrowth and subsequent microbial translocation [21]. Chronic narcotic treatment significantly alters gut microbial composition and induces expansion of Gram-positive pathogenic and a reduction in bile acid bacterial strains. A significant reduction in both primary and secondary bile acid levels was seen in the gut. In animals, narcotic-induced microbial dysbiosis could be counterbalanced by fecal microbiota transplantation [29].

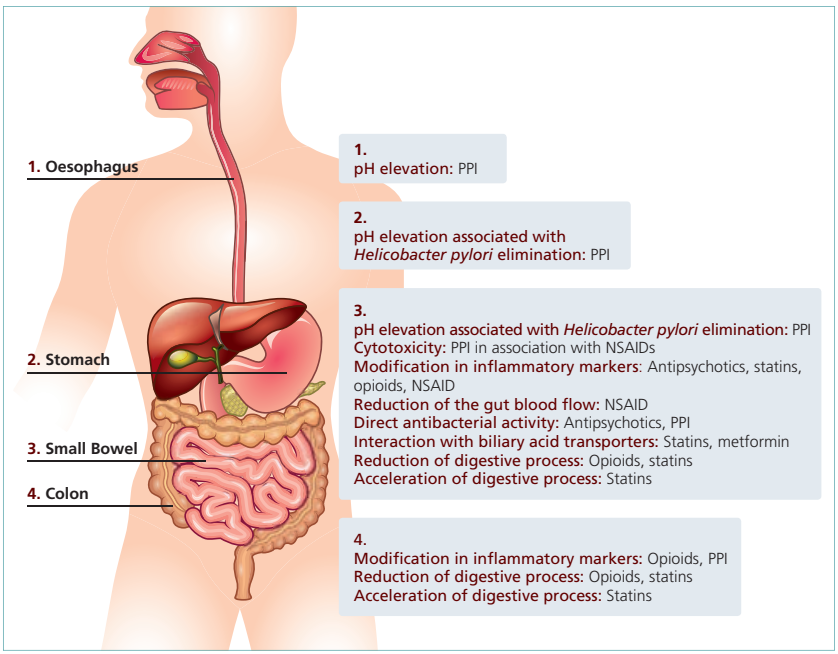


Figure 6: *Proposed mechanisms by which drugs influence the gut microbiome (from Le Bastard* et al. *[21])*

Statins

The interactions between statins and bile acids, which share transporters in the intestine, may underlie the interplay between statins and gut microbial composition. Moreover, data suggest that statins have direct anti-bacterial activity that may explain some shifts in the gut microbiome [21].

Conclusions

Drugs and diet can affect the microbiome and further research is needed on how to precisely alter the microbiome for therapeutic effect. In addition, they should be duly taken into account as important covariates in the interpretation of the results of microbiota studies, performed in different subject and/or patient populations.

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CURRENT AND FUTURE
MANAGEMENT OF DIGESTIVE
DISEASE: FROM BENCH TO BEDSIDE

Notes


Colm O'Morain

11:00 Influence of *Helicobacter* Infection and its Eradication on Gut Microbiota

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Introduction

Initially, the stomach was considered to be completely sterile due to its acidic environment [1]. Following the seminal discovery of *Helicobacter pylori* [2], it was thought to be the only bacterium capable of colonising the human stomach based on the ability of *H. pylori* urease to neutralise stomach acid. We now know that approximately half of the world's population are infected with *H. pylori*. Infection is thought to occur in early childhood and persists for life if left untreated [3]. *H. pylori* infection causes chronic gastritis, the development of duodenal or gastric ulcers in up to 10 % of patients, gastric cancer in up to 3 % of patients and mucosa-associated lymphoid tissue lymphoma in <0.01 % of patients [4]. Disease outcome is associated with host, bacterial and environmental factors. Treatment for *H. pylori* involves an anti-secretory drug together with 2 or 3 antimicrobials. Consensus Guidelines recommend that the local prevalence of antibiotic resistance is considered when choosing an appropriate treatment regimen. Clarithromycin-based first-line triple therapy should be avoided in areas where the prevalence of clarithromycin-resistant infections is greater than 15% and either bismuth quadruple therapy or non-bismuth quadruple, concomitant therapies for 14 days are recommended [5,6].

Recently, advanced molecular-based methods have shown that the normal stomach is host to far more microorganisms than previously believed, although the role of the gastric microbiome in health and disease is not yet fully understood. Additionally, studies into the composition of the intestinal microbiota and its impact on human health has gained striking appreciation in recent years and is now thought to play an integral role in energy metabolism, absorption of nutrients and invasion of pathogens [7]. It has emerged that *H. pylori* infection influences both the gastric and intestinal microbiome. Moreover, the microbiome is altered as a direct consequence of *H. pylori* treatment. The balance and diversity of an individual's gastric microbiome, and any alterations as a result of *H. pylori*-infection, are clinically important based on the potential to influence disease outcome. Further, changes in the microbiome in response to the broad-spectrum antibiotics and/or anti-secretory drugs may influence gut dysbiosis, adverse events to *H. pylori* eradication therapy, as well as the pathogenesis of infection.

Influence of *H. pylori* Infection on the Gut Microbiota

Molecular-based studies on the gastric microbiota have revealed a previously unappreciated richness of the bacterial flora, including bacteria belonging to *Proteobacteria, Firmicutes, Actinobacteria, Bacteroidetes* and *Fusobacteria phyla* [8]. These phyla are represented mainly by the genera *Streptococcus, Lactobacillus, Veillonella, Clostridium, Prevotella, Porphyromonas, Rothia, Neisseria* and *Haemophilus* [8-10]. Moreover, variations in the most abundant bacteria from person-to-person have been reported [8]. Changes in the gastric environment due to *H. pylori* infection or long-term PPI use are likely to impact the structure of the microbiota community [11,12]. Studies in mice have shown that *H. pylori* infection leads to significantly different population structures in both the stomach and intestinal microbiota [13]. Sequencing methods using human samples have shown that *H. pylori* completely dominates the gastric microbiota in infected individuals [11,14-16] and, interestingly, *H. pylori* has also been detected in individuals deemed *H. pylori*-negative by conventional methods (Figure 1) [8,11,15].

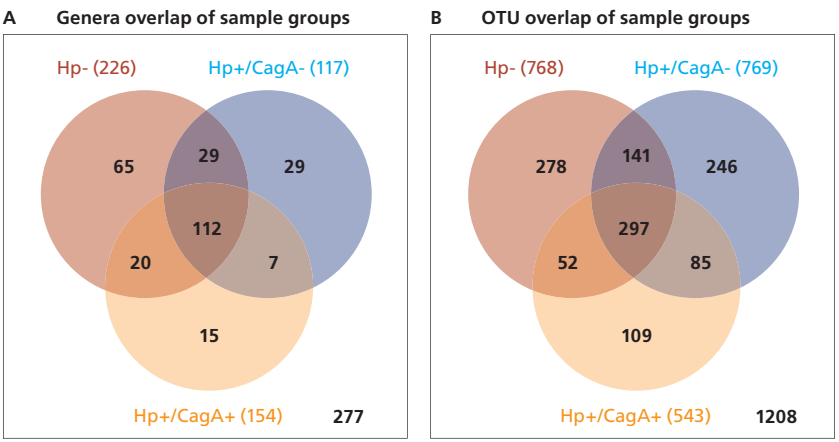

Figure 1: *Venn diagram visualizing the number of* **A**) *group specific genera and* **B**) *operational taxonomical units (OTUs) (from Klymiuk* et al. *[16])*

There have been conflicting reports on the impact of *H. pylori* abundance on gastric microbiome diversity, with some studies finding no difference between infected and uninfected patients [8,11] and others showing decreased diversity during *H. pylori* infection (Figure 2) [7,9,15,16]. Studies have also characterised the microbiota at different stages of *H. pylori*-associated disease, with some indicating a reduction of bacterial diversity in progression from gastritis to cancer (Figure 3) [15,17] and others reporting an increase in diversity [18]. Factors such as anatomical location of the

sample analysed, microbiota detection method or study population may account for such differences in results. The idea that gastric microbial diversity could influence *H. pylori*-induced gastric cancer progression is attractive. Indeed, it has been suggested that the lower microbial diversity in the upper digestive tract is associated with lower pepsinogen I/II ratio, which is an indicator of increased gastric cancer risk [19]. Further insight into the gastric microbiome and it's modulation by *H. pylori* will reveal the potential of clinically targeting the microbiome to prevent the development of gastric cancer.

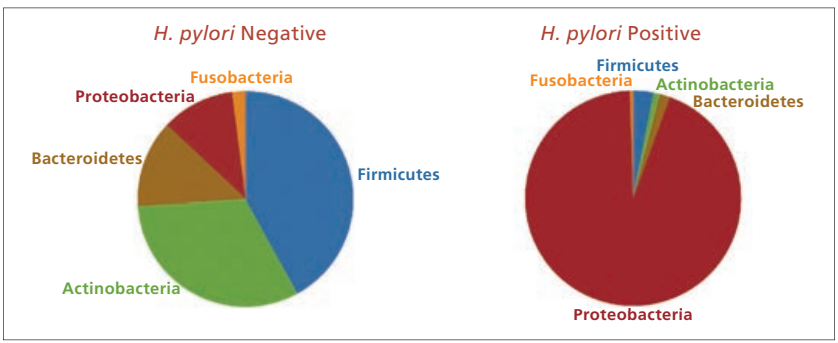

Figure 2: *Alterations in the gastric microbiota following* Helicobacter pylori *infection (from Noto & Peek [7])*

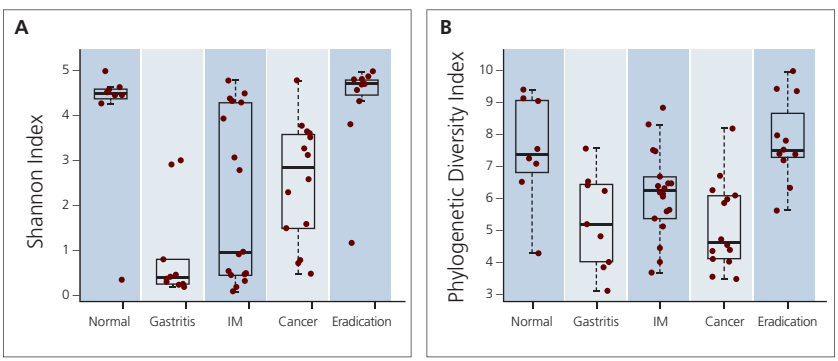

Figure 3: *Alpha diversity in different groups* **A**) *Boxplot of Shannon index in different groups. The boxes denote interquartile ranges (IQR) with the median as a black line and whiskers extending up to the most extreme points within 1.5 fold IQR* **B**) *Boxplot of phylogenetic diversity index in different groups. The meaning of box is the same with A (from Li* et al. *[15])*

Influence of *H. Pylori* Eradication on the Gut Microbiota

H. pylori eradication requires antimicrobials and acid suppression. Intestinal disorders such as diarrhoea are a common side effect of *H. pylori* treatment, indicating a dysbiosis of the intestinal microbiota [20]. In addition, the use of probiotics such as *Lactobacillus* sp. or *Saccharomyces boulardii* contributes to a decrease in the diarrheal incidence and an improvement in treatment compliance and possibly its efficacy (Table 1) [21-23].

Table 1: Lactobacilli as *add-on* medication to triple therapies for *H. pylori* eradication: a meta-analysis (from Zou *et al.* [22])

End-point	OR	95% C.I.
Eradication Rate	1.78	1.21-2.62
Incidence of Diarrhea	0.23	0.11-0.48
Incidence of Bloating	0.41	0.23-0.75
Incidence of Taste Disturbance	0.23	0.11-0.47

Recently, there has been interest in the impact of *H. pylori* therapies on the short- and long-term stability of the microbiota (Table 2) [24].

Table 2: Effect of 7-day triple therapy (lansoprazole+clarithromycin+amoxicillin) on fecal microbiota evaluated by the *FISH* Technique* (from Myllyluoma *et al.* [24])

Microbial population	Day 0	Day 7	Day 28	Day 70
Total cell count	11.4 ± 0.04 (20)	10.9 ± 0.07 (20)*	11.2 ± 0.03 (20)	11.2 ± 0.03 (20)
Bifidobacteria	8.8 ± 0.22 (20)	6.5 ± 0.15 (20)*	7.3 ± 0.19 (20)*	7.9 ± 0.22 (20)*
Lactobacilli/enterococci	8.5 ± 0.16 (20)	7.5 ± 0.14 (20)*	7.5 ± 0.10 (20)*	7.9 ± 0.10 (20)*
Bacteroides fragilis Bacteroides distasonis	9.7 ± 0.16 (20)	8.7 ± 0.26 (20)*	9.1 ± 0.13 (20)*	9.4 ± 0.11 (20)
Clostridium histolyticum	7.3 ± 0.15 (20)	6.3 ± 0.16 (13)*	7.3 ± 0.12 (20)	7.2 ± 0.11 (20)
Eubacterium rectale Clostridium coccoides	10.0 ± 0.13 (20)	8.8 ± 0.22 (20)*	10.1 ± 0.06 (20)	10.2 ± 0.06 (20)
Faecalibacterium prausnitzii	9.5 ± 0.27 (20)	8.0 ± 0.45 (13)*	8.7 ± 0.31 (19)*	8.9 ± 0.33 (18)*

[a] Data are given as mean count (log_{10} colony-forming units/g wet weight of faeces) ± standard error of the mean - * $p<0.001$ compared with Day 0 (baseline)

* FISH = Fluorescence *In Situ* Hibridisation

Indeed, alterations in throat, stomach and intestinal microbiota have been reported in response to different *H. pylori* treatment regimens. Analysis of stool samples has shown that 7 days clarithromycin-based triple therapy perturbs the gut microbiome, specifically affecting the abundance of *Bacteriodetes* and *Firmicutes* (Figure 4) [25,26].

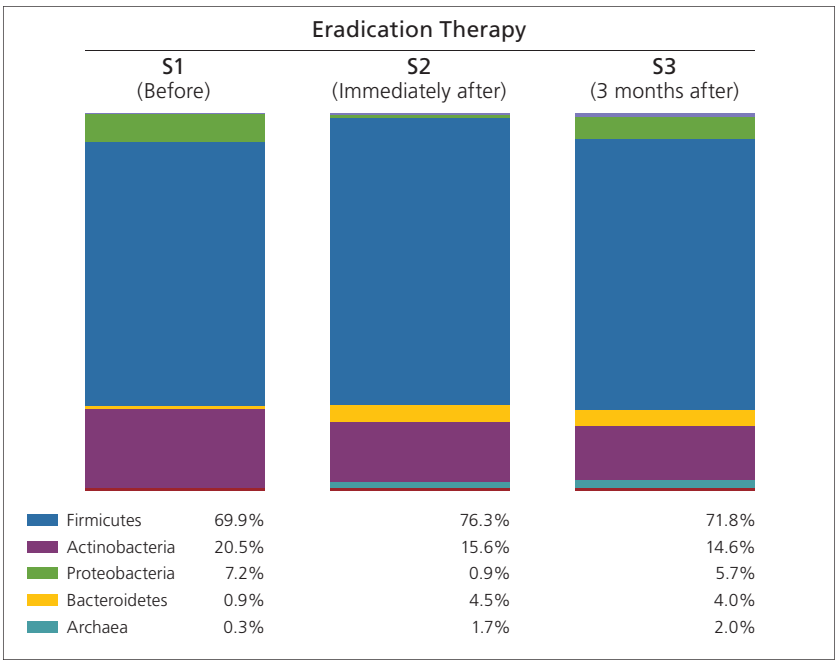

Figure 4: *Proportion of the dominant five phyla in the faecal samples after eradication therapy. The percent proportions of the five dominant phyla of Firmicutes, Actinobacteria, Proteobacteria, Bacteroidetes and Archaea in all faecal samples at S1, S2 and S3 are depicted in the bar charts. The S1, S2 and S3 samples include 984 296, 1 187 681 and 1 022 232 high-quality reads, respectively. (from Yanagi* et al. *[24])*

A study from China reported changes in the composition of the microbiome in the corpus, antrum and stool samples of duodenal ulcer patients following treatment with a proton pump inhibitor, bismuth, clarithromycin and amoxicillin for 10 days [27]. *H. pylori* infection suppressed gastric colonization with *Lactobacillus* group, *Clostridium leptum* subgroup and *Enterobacteria*. Interestingly, there were also differences in the

bacterial composition between male and female patients [27]. Bismuth quadruple therapy has also been reported to lead to dysbiosis of the gut microbiota, with an increased relative abundance of *Proteobacteria* and decreased relative abundances of *Bacteroidetes* and *Actinobacteria* [28]. Concomitant therapy has been shown to alter both the gut and throat microbiota [29]. On-going multi-centre European research involving Francis Megraud (France), Teresa Alarcón (Spain), Lars Engstrand (Sweden), Antonio Gasbarrini (Italy), Javier Gisbert (Spain), Adrian McNicholl (Spain) and Colm O'Morain (Ireland), sponsored by the European *Helicobacter* Microbiota Study Group, aims to provide further insight into changes in the microbiota in the European population by analysing stool and biopsy samples 6 months post-treatment with either bismuth quadruple therapy or concomitant therapy.

Analysis of alterations in the microbiota in response to *H. pylori* therapies has the potential to identify trends in microbiota populations that may predict adverse events. Additionally, the distribution of antibiotic resistance in microbial communities following antibiotic therapy may be evaluated. Indeed, an increased level of antibiotic resistance rates was detected for *Enterobacteriaceae, Enterococcus* spp. and *Bacteroides* spp. following concomitant eradication therapy [29]. These findings highlight the concern of wide-spread use of broad spectrum antibiotics on the selection of resistant infections.

Future Perspectives

Research into the impact of *H. pylori* and its eradication on the gut microbiota is still in its infancy. Further studies are required to identify significant associations between the microbiota population and gastric cancer risk, in order to:

- identify microbial signatures associated with disease risk
- reveal the potential for clinically modifying the microbiome in order to prevent disease progression

Additional investigation into the short-term dysbiosis of the gut microbiome in response to the various *H. pylori* therapies may reveal microbiota populations associated with adverse events to a given treatment. Of importance, the long term impact of *H. pylori* eradication is of interest, given the close link between gut microbiota homeostasis and human health. Increased investigation into the effect of acid suppression following *H. pylori* therapy is also warranted, given recent (albeit debated) evidence linking long-term PPI use with gastric cancer risk [30]. Finally, there is a strong rationale for considering the influence of *H. pylori* treatment on gut dysbiosis and the selection of antibiotic resistant bacterial strains in high risk gastric cancer regions, where mass screening and eradication are performed.

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Mario Guslandi

11:30 Microbiota-directed Therapies in Digestive Disease
Focus on Probiotics and Chronic Intestinal Disorders

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Introduction

Probiotics are considered nowadays potentially useful in various diseases but, obviously enough, it is their possible beneficial role in the digestive tract which has especially been the object of speculation and clinical evaluation.

In particular probiotics appear potentially helpful in treating chronic intestinal disorders, where an imbalance in the composition of the gut microbiota – so-called dysbiosis – has been reported, such as inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS), or where intestinal bacteria can play an active role in inducing inflammation (diverticular disease). In addition to their potential ability to correct dysbiosis and to direct inhibit some intestinal pathogens, probiotics may exert beneficial effects in the gut by stimulating local immunity and counteracting the effects of pro-inflammatory cytokines. Despite the enormous interest by both researchers and physicians in this area, controlled clinical trials are comparatively scarce, thus impeding, in some instances, to reach definitive conclusions.

As will be discussed below, rather surprisingly the number of meta-analyses seems occasionally to almost equate the number of eligible controlled studies, which, again, prevents to offer reliable advise to the clinicians, because probiotics are not all alike and physicians should be made able to choose the right product to meet the needs of the single patient.

Inflammatory Bowel Disease

The role of the gut microbiota, or, more exactly, of its alterations in promoting and maintaining inflammation in IBD is now widely recognized.

In particular, several studies, although carried out by means of different methods, have been able to pinpoint the kind of dysbiosis [1-3], affecting the gut of patients with either ulcerative colitis (UC) or Crohn's disease (CD). For instance, a significant reduction in the intestinal amount of *Firmicutes* (especially *Faecalibacterium Prausnizii* and *Bacteroides fragilis* and of *Bifidobacteria*) has been observed. By contrast, an increased presence of *Campylobacter concisus* and *Enterococcus faecium* has been

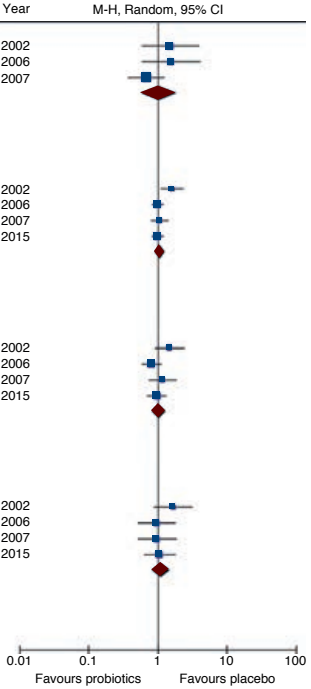
reported. Others have found a decreased abundance of *Prevotella* and *Butyricimonas* both in inflamed and non-inflamed mucosal areas in UC patients.

Various placebo-controlled clinical trials carried out both in adults and in children with Crohn's disease have investigated the possible efficacy of various strains of Lactobacilli, administered for periods of up to 24 months in preventing post-surgical clinical or endoscopic recurrence. In no instance the probiotic resulted superior to placebo.

Therefore a meta-analysis [4] confirmed the ineffectiveness of Lactobacilli in this respect (Table 1).

Table 1: Forest plot of randomised controlled trials reporting the efficacy of probiotics *vs* placebo in preventing clinical or endoscopic relapse in CD in remission following a surgical resection (from Derwa *et al.* [4])

Study or subgroup	Probiotics Events	Total	Placebo Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Year
3.1.1 Clinical relapse of disease activity							
Prantera (2002)	8	23	5	22	26.9%	1.53 [0.59, 3.97]	2002
Marteau (2006)	9	48	6	50	26.8%	1.56 [0.60, 4.06]	2006
Van Gossum (2007)	11	34	17	36	46.4%	0.69 [0.38, 1.24]	2007
Subtotal (95% CI)		105		108	100.0%	1.06 [0.59, 1.92]	
Total events	28		28				
Heterogeneity: τ^2=.11, χ^2=3.19, df=2 (*P*=.20), I^2=37%							
Test for overall effect: *Z*=.19 (*P*=.85)							
3.1.2 Endoscopic relapse of disease activity (Rutgeerts score 1 or more)							
Prantera (2002)	22	23	13	22	15.4%	1.62 [1.13, 2.32]	2002
Marteau (2006)	39	48	41	50	30.7%	0.99 [0.82, 1.20]	2006
Van Gossum (2007)	26	34	26	36	21.5%	1.06 [0.80, 1.39]	2007
Fedorak (2015)	47	58	50	62	32.4%	1.00 [0.84, 1.20]	2015
Subtotal (95% CI)		163		170	100.0%	1.09 [0.92, 1.29]	
Total events	134		130				
Heterogeneity: τ^2=.02, χ^2=6.32, df=3 (*P*=.10), I^2=53%							
Test for overall effect: *Z*=.98 (*P*=.33)							
3.1.3 Endoscopic relapse of disease activity (Rutgeerts score 2 or more)							
Prantera (2002)	17	23	11	22	18.0%	1.48 [0.91, 2.40]	2002
Marteau (2006)	26	48	33	50	30.7%	0.82 [0.59, 1.14]	2006
Van Gossum (2007)	19	34	17	36	19.6%	1.18 [0.75, 1.87]	2007
Fedorak (2015)	32	58	35	62	31.7%	0.98 [0.71, 1.34]	2015
Subtotal (95% CI)		163		170	100.0%	1.04 [0.82, 1.31]	
Total events	94		96				
Heterogeneity: τ^2=.02, χ^2=4.43, df=3 (*P*=.22), I^2=32%							
Test for overall effect: *Z*=.30 (*P*=.77)							
3.1.4 Endoscopic relapse of disease activity (Rutgeerts score 3 or more)							
Prantera (2002)	14	23	8	22	21.5%	1.67 [0.88, 3.18]	2002
Marteau (2006)	14	48	15	50	23.8%	0.97 [0.53, 1.79]	2006
Van Gossum (2007)	12	34	13	36	22.5%	0.98 [0.52, 1.83]	2007
Fedorak (2015)	19	58	19	62	32.2%	1.07 [0.63, 1.81]	2015
Subtotal (95% CI)		163		170	100.0%	1.13 [0.84, 1.52]	
Total events	59		55				
Heterogeneity: τ^2=.00, χ^2=1.92, df=3 (*P*=.59), I^2=0%							
Test for overall effect: *Z*=.79 (*P*=.43)							
Test for subgroup differences: χ^2=.22, df=3 (*P*=.97), I^2=0%							



A recent multicenter trial of the probiotic mixture VSL#3 also failed to show a significant effect compared with placebo [5].

Likewise, a large French randomized trial comparing *Saccharomyces boulardii* alone and placebo observed no differences between the two groups [6], whereas it appears that adding that probiotic to mesalazine significantly reduces the recurrence rate compared with mesalazine alone [7].

All in all, probiotics do not seem to play a role in the treatment of Crohn's disease. By contrast, UC patients can benefit by some types of probiotic agents. Controlled clinical trials *versus* mesalazine in the maintenance treatment of ulcerative colitis have repeatedly found that the two treatments have comparable efficacy in maintaining clinical remission for up to 12 months [8], which suggests the possibility to use the probiotic in patients who are intolerant to mesalazine.

When added to mesalazine, the VSL #3 mixture is significantly superior to placebo plus mesalazine in maintaining remission in children with UC (Table 2) [8,9-11].

Table 2: Probiotics in ulcerative colitis maintenance

E. Coli Nissle 1917 *versus* Mesalazine at 12 months (Rembacken *et al.*, 1999 [9] Kruis *et al.*, 2008 [8])
L.GG versus Mesalazine *versus L.GG*+Mesalazine at 6 and 12 months (Zocco *et al.*, 2006 [10])
VSL#3+ Mesalazine *versus* Placebo+Mesalazine at 12 months (children) (Miele *et al.*, 2009 [11])

A recent double-blind, placebo-controlled trial, performed in India and addressing the possible role of VSL#3 in active, mild to moderate UC, observed both at 6 and 12 weeks a significantly superior effect of the probiotic in inducing remission and in improving the disease activity score [12].

In UC patients, undergoing restorative proctocolectomy with ileal pouch-anal anastomosis , acute inflammation of the pouch ("pouchitis") can develop in 24-60% of cases. Antibiotic treatment is usually effective but recurrence is the rule in up to 60% of cases. VSL# 3 is the only probiotic agent found to be able, in monotherapy, to maintain remission and prevent relapses of pouchitis [13].

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a multifactorial clinical condition, the main symptoms of which (abdominal pain, diarrhea and/or constipation, bloating) can be related,

among other factors involved, to intestinal dysbiosis. In addition to post-infectious IBS and the possible existence of a small intestine bacterial overgrowth (SIBO), IBS patients generally show signs of intestinal dysbiosis such as reduced fecal concentrations of *Lactobacilli, Bifidobacteria* and of *Faecalibacterium prausnitzii* [14]. Thus, from a theoretical point of view, probiotics could be potentially useful also in IBS treatment, especially in the diarrhea-predomint subtype.

Unfortunately, in clinical practice there are no objective parameters to judge the efficacy of a medical treatment for IBS, except symptom relief. Therefore, all clinical studies carried out in this disorder have employed, as treatment endpoints one or more symptoms (bloating, diarrhea, discomfort or pain) or, in alternative, some kind of overall score, including the all above symptoms.

If we add the fact that trials with probiotics in IBS have employed different products, in different doses and for different length of time, it is clear that the results are so heterogeneous to hamper the possibility to reach definitive conclusions [15,16]. For instance the placebo-controlled studies employing different strains of Lactobacilli have provided extremely variable and conflicting results (Table 3) [17-24].

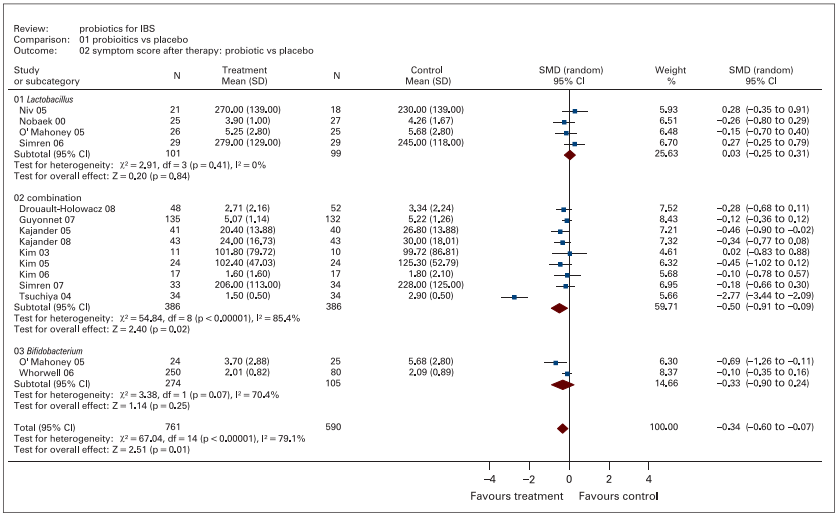
Table 3: Probiotics for IBS: double-blind RCTs *Lactobacillus* (L) *versus* placebo (PL)

Lactobacillus plantarum	**Patients (n)**	**Results**	
Nobaek *et al.*, 2000 [17]	60	L > PL bloating L = PL abdominal pain	
Sen *et al.*, 2002 [18]	12	L > PL bloating	
Niedzielin *et al.*, 2001 [19]	40	L > PL abdominal pain	
Lactobacillus GG			
O'Sullivan & O'Morain, 2000 [20]	24	L = PL global	
Bausserman & Michail, 2014 [21]	50	L = PL global	children
Gawrońska *et al.*, 2007 [22]	37	L > PL pain frequency L = PL pain severity	children
L. Acidophilus SDC 2012-2013			
Sinn *et al.*, 2000 [23]	40	L > PL abdominal pain	
Lactobacillus reuteri			
Niv *et al.*, 2005 [24]	54	L = PL global	

Various meta-analyses, pooling the data from the available studies in which a probiotic agent was administered *(Lactobacilli, Bifidobacteria, Saccharomyces boulardii, probiotic mixtures of various type)* have concluded that probiotics as a group, are useful in ameliorating symptoms in IBS patients [25-27]. Interesting as this can be, the practical value of this statement for the practitioner is questionable, because it would promote the wrong impression that probiotics are all alike and that any product could be beneficial.

A more detailed, subsequent meta-analysis, has actually shown that the benefits of probiotics in treating IBS symptoms apply only to *Bifidobacteria*, either employed alone or in association with other strains (Table 4) [28].

Table 4: Forest plot of trials comparing probiotics with placebo reporting a continuous outcome (IBS, irritable bowel syndrome; SMD, standardised mean difference) (from Moayyedi *et al.* [28])



Even so, it remains unclear what are the effective doses and the ideal duration of treatment, when prescribing products containing *Bifidobacteria* to subjects suffering from IBS.

A recent international consensus conference on the role of probiotics in the management of lower gastrointestinal symptoms could add very little to what was already

known as for a gut functional disorder such as IBS [29]. Not surprisingly, the ACG Monograph on the management of irritable bowel syndrome, published in the current year, although suggesting again that probiotics – as a group – can improve IBS symptoms, has defined the recommendation as "weak" and the quality of evidence "low" [30].

Diverticular Disease

The role of the gut microbiota in diverticular disease is now widely accepted. Inflammation of diverticula is caused or promoted by intestinal bacteria, so much so that acute diverticulitis is treated with antibiotics and among the various tools to try to prevent diverticulitis in some countries (e.g. Italy) a poorly absorbable antibiotic such as rifaximin is widely employed. Although diverticular disease is often asymptomatic, diverticulitis can occur in up to 25% of cases, and complications such as perforation, obstruction, abscesses and fistulae are possible.

In clinical practice we are mostly dealing with symptomatic uncomplicated diverticular disease (SUDD), a scenario where the use of probiotic agents can have a rationale. In addition to the fact that the gut microbiota is involved in the development of diverticulitis, dysbiosis is supposed to be present also in SUDD. Higher amounts of *Enterobacteriace* in the stools of such patients have been reported. Moreover, a study of the fecal microbiota in patients with recent diverticulitis found a higher abundance of *Pseudobutyrivibrio* and *Bifidobacteria* and determined a possible correlation between abdominal pain and relative abundance of Cyanobacteria, and between bloating and abundance of *Ruminococcus* and reduction of *Roseburia* [31].

Most controlled studies in SUDD have employed probiotics co-administered with mesalazine, showing that, for instance, that both the combination of *Lactobacillus casei* plus mesalazine for up to 24 months and of VSL#3 plus balsalazide for 12 months are significantly more effective than the single agents in reducing symptoms and preventing recurrence of diverticular inflammation (Table 5) [32-35].

Table 5: Probiotics + 5-ASA in diverticular disease

L. casei + Mesalazine for 12 months > single agents on symptoms and recurrence rate (Tursi *et al.*, 2006 [32])
L. casei + Mesalazine for 12-24 months > single agents on recurrence rate (Tursi *et al.*, 2008 [33])
VSL#3 + Balsalazide for 12 months > single agents on recurrence rate (Tursi *et al.*, 2007 [34])
B. infantis + Mesalazine *versus* Mesalazine alone > Placebo on symptoms (Stollman *et al.*, 2013 [35])

A multicenter trial including more than 200 patients, confirmed that both *Lactobacillus casei*, mesalazine and their combination are significantly better than placebo [36]. However, a recent double-blind multicenter study comparing mesalazine in different doses with placebo for 48-96 weeks in the prevention of acute diverticulitis failed to show any statistical difference [37,38] which makes it harder to give a proper interpretation of the results concerning the association of mesalazine and probiotics.

Thus, although the rationale of prescribing probiotics in patients with SUDD to treat symptoms and prevent relapses appears sound enough, the current evidence remains fogged, and all systematic reviews agree that definitive conclusions cannot be drawn [39-41] and that further studies, employing probiotics *alone*, are necessary.

Conclusions

Humans and microbes have established a symbiotic association over time, and perturbations of this association have been linked to several digestive diseases, both organic and functional. The existence of dysbiosis in chronic intestinal disorders constitutes a good rationale for employing probiotics in diseases such as IBD, IBS and SUDD.

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David Armstrong

12:00 Fecal Microbiota Transplantation: Beyond *C. difficile* Infection

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Introduction

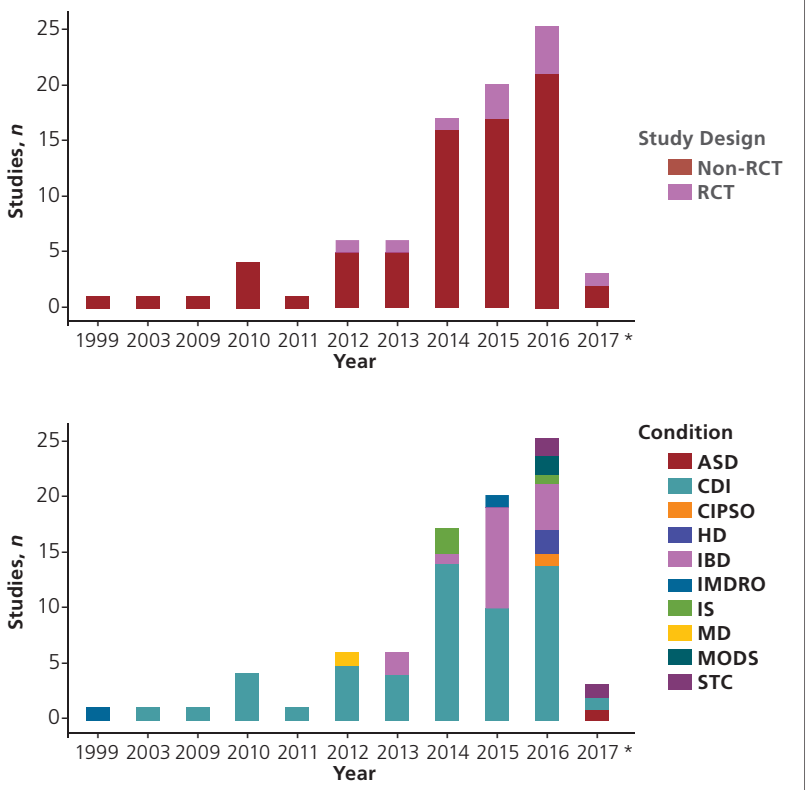
An increasing number of conditions, including *Clostridium difficile*-infection (CDI) or *C. difficile*-associated diarrhea (CDAD), inflammatory bowel disease (IBD), irritable bowel syndrome (IBS) and post-infectious and post-antibiotic functional gastrointestinal disorders (FGID), as well as obesity and metabolic syndrome and extra-gastrointestinal disorders (anxiety, depression, asthma, autism) have been attributed or linked to dysbiosis or disturbances of the human gastrointestinal (GI) microbiome [1]. This has led to burgeoning interest in the therapeutic modification of the GI microbiome by various means, including dietary changes and the use of prebiotics, probiotics, antibiotics or synbiotics (i.e. prebiotic plus probiotic) to increase the number or proportion of resident, beneficial bacteria and, in severe conditions, such as CDI, fecal microbiota transplantation or transfer (FMT) to replace the abnormal host microbiome with the microbiota of a healthy donor.

FMT offers the opportunity to induce a major, enduring change to the host microbiome and it has proven very effective in the management of recurrent CDI [1,2]. These results have engendered increasing optimism that microbiome modification will lead to comparable improvements in outcomes for the many other conditions, attributed to GI dysbiosis, and this optimism extends beyond the medical profession to practitioners of alternative medicine and, patients, themselves, some of whom have provided on-line documentation of unsupervised, self-administered FMT in the home. The number of published studies has increased dramatically in less than a decade although, to date, few have been randomized controlled trials (Figure 1) [3].

Dysbiosis-linked Conditions

Clostridium difficile-*associated Diarrhea or* C. difficile-*infection*

The incidence of CDI hospitals has increased dramatically over the last 2-3 decades, as has the severity of the associated illnesses, with an estimated inpatient mortality of about 5% and an all-cause mortality of over 15% [4]. Antibiotic therapy with metronidazole, vancomycin or fidaxomicin is effective in a proportion of cases



ASD = autism spectrum disorder; **CDI** = Clostridium difficile infection; **CIPSO** = chronic intestinal pseudo-obstruction; **FMT** = fecal microbiota transplantation; **HD** = hepatic diseases; **IBD** = inflammatory bowel disease; **IMDRO** = infection with multidrug-resistant organisms; **IS** = immunodeficiency syndrome; **MD** = metabolic disease; **MODS** = multiple organ dysfunction syndrome; **RCT** = randomized controlled trial; **STC** = slow transit constipation.

* Number of studies between 1 January and 31 January 2017; 3 studies included

Figure 1: *Number of human clinical studies dealing with fecal microbiota transplantation over the last decades (from Bafeta* et al. *[3])*

but the emergence of more toxic, antibiotic-resistant strains has resulted in treatment failure or CDI recurrence in an increasing proportion of patients. FMT is, now, recognized as an important and effective strategy for CDI although there is continuing debate regarding the precise indications for FMT, the most appropriate route of administration, the likelihood of treatment response and the potential for adverse events. A recent systematic review and meta-analysis of 5 randomised controlled trials reported that FMT was statistically, significantly more effective than placebo or vancomycin for the treatment of CDI (RR 0.41, 95% CI 0.22-0.74; NNT 3, 95% CI 2-7) although there was significant heterogeneity related to the administration mode and trial location [2] with the need for further studies to optimise FMT preparation and administration mode. Recent guidelines are, generally, in agreement in recommending that FMT be considered for patients with two or more recurrences and who have recurred after a vancomycin taper [5], for patients with multiple recurrences of CDI who have failed appropriate antibiotic treatments [6] or for appropriate patients with recurrent CDI regardless of other comorbidities [7]. These recommendations, notwithstanding, there remain gaps with respect to clear definitions of recurrent CDI and CDI severity, the definitions of treatment success or failure, the documentation of adverse outcomes, the determination of the most appropriate modes of FMT administration and the identification of microbiome, donor and host factors associated with treatment outcomes.

Non-CDI Gastrointestinal Diseases

The success of FMT for the treatment of recurrent CDI has led to studies of its use for other gastrointestinal conditions, including inflammatory bowel disease (ulcerative colitis – Crohn's disease), functional bowel disorders, hepatic encephalopathy and metabolic syndrome.

Inflammatory Bowel Diseases

Currently, medical treatment for inflammatory bowel diseases (IBD) is grounded in the suppression of the host's immune response with the goal of inducing remission and preventing relapse for what is considered to be a chronic, incurable condition attributable to a dysfunctional interaction between some ill-defined aspects of the host's genetics, microbiome and environment. The most prevalent theory is that the aberrant immune response is a consequence of an abnormal gut microbiome or dysbiosis and, in support of this, systematic reviews indicate that antibiotics can induce remission of both ulcerative colitis and Crohn's disease [8]. However, although the gut microbiome in IBD patients differs from that of healthy controls, it has not been possible to identify a specific microbiological target for therapy [9]. An alternative approach is to normalise the microbiome, analogous to the treatment of recurrent CDI, by FMT from a healthy individual.

Ulcerative Colitis

Successful FMT was first described for the treatment of ulcerative colitis (UC) in a case report, nearly 3 decades ago [10] and a systematic review of later case series reported a pooled remission rate of 24% (95% CI: 11-45%) for 27 UC patients in 4 reports [11]. A systematic review and meta-analysis of subsequent *high-quality* studies identified 4 randomized, placebo-controlled trials of FMT for active ulcerative colitis involving a total of 277 participants [12]. The pooled rates for combined endoscopic and clinical remission were 27.9% for FMT compared with 9.5% for the control intervention for an NNT of 5 (95% CI: 4 -10); the pooled risk ratio for failure to achieve combined endoscopic and clinical remission was 0.80 (95% CI: 0.71-0.89; p<0.0001), favouring FMT over control (Figure 2).

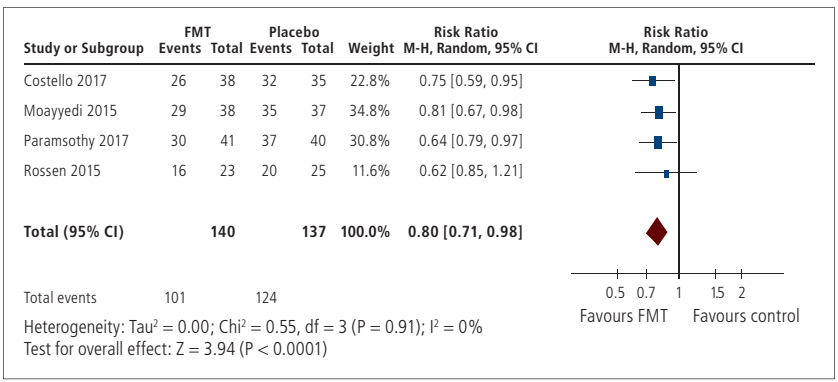


Figure 2: *Forrest plot of the meta-analysis of all studies reporting combined clinical remission with endoscopic remission or response for FMT in ulcerative colitis in randomized, placebo-controlled studies (from Narula* et al. *[12])*

Crohn's Disease

There have been no randomized, placebo-controlled studies of FMT in Crohn's disease (CD) but a recent systematic review of 83 CD patients in 11 studies, including 4 case reports and 7 prospective, uncontrolled cohort studies suggested that about one-half to two-thirds of FMT recipients achieve remission; a meta-analysis of 6 eligible cohort studies (Figure 3) indicated a response rate of 51.8% (95%CI: 31.1-71.9%) although it is probable that this is an overestimate of the effect size as these were all small, uncontrolled studies [13]. There are, now, randomized controlled trials in progress for CD although study design and interpretation of the results must accommodate the varied phenotypic presentations of CD, compared with UC, and the consequent

implications for the mode of FMT administration. FMT can be administered via the oral or nasogastric routes for CD patients with small bowel involvement whereas it must be administered to the colon for UC patients.

Studyname	Event rate	Lower limit	Upper limit	Total
Cui	0.767	0.585	0.884	23/30
Suskind	0.556	0.251	0.823	5/9
Vermeire	0.071	0.004	0.577	0/6
Wei	0.125	0.007	0.734	0/3
Vaughn	0.526	0.311	0.732	10/19
Goyal	0.500	0.123	0.877	2/4
Random	0.518	0.311	0.719	

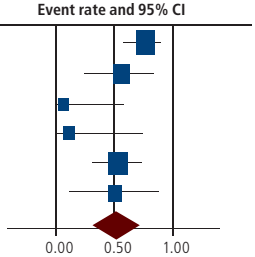


Figure 3: *Forest plot of the meta-analysis of clinical remission and faecal microbiota transplantation [FMT] in Crohn's disease including available cohort studies to date. The pooled proportions with 95% confidence intervals [CIs] were calculated using the random effects model (diamond). The filled squares represent the studies in relation to their weights (from Paramsothy* et al. *[13])*

In summary, there is some indication that FMT may be beneficial in IBD, the evidence being stronger for UC than for CD. However, the magnitude of the benefit remains uncertain, as does the duration of effect and there is no consensus on the optimal FMT strategies for achieving and, then, maintaining remission for IBD. For example, in comparison with FMT for CDI, successful FMT for IBD seems to require a greater number of transfers and, possibly, restriction to specific, *super-donors*. For these reasons, and others, the recent BSG / HIS Guidelines do not recommend FMT as treatment for IBD or, indeed for any other gastro-intestinal or non-gastro-intestinal disease [7]. In special cases, the authors do, however, recommend that FMT should be offered to patients who have recurrent CDI and IBD, but they advice that patients should be counselled about a small but recognized risk of exacerbation of IBD [7].

Pouchitis

Pouch inflammation develops in more than half of patients who have undergone restorative colectomy with ileal pouch anal-anastomosis; the hypothesis that pouchitis is caused by an abnormal immune response to the gut microbiota is supported by evidence of microbial changes in pouchitis and good clinical responses to antibiotics or probiotics [14]. However, there is limited evidence to support FMT for this condition; no response was reported after 4 weeks in one pilot study of 8 patients whereas 71%

global symptom improvement was reported after 4 weeks in another pilot study of 9 patients and cure or sustained response was reported in 4 of 6 patients in 2 case series. To date, there have been no randomized controlled trials of FMT for pouchitis.

Functional Gastrointestinal Disorders

Irritable Bowel Syndrome

There is a number of mechanisms whereby the microbiome might influence the pathogenesis of irritable bowel syndrome (IBS) (Figure 4) including effects on intestinal permeability and barrier function, immune function, GI sensorimotor function and the gut-brain axis [15]. Furthermore, a number of studies has reported that IBS patients have an abnormal microbiome or dysbiosis. This raises the possibility that restoration of a normal microbiome may lead to an improvement in IBS symptoms; however, as in IBD, the nature of the dysbiosis is unclear since no specific bacterial species have been linked consistently to the presence of IBS symptoms or their response to therapy. In the absence of a specific therapeutic target, FMT offers the possibility of normalising the microbiome in IBS patients by transplanting stool from healthy individuals who have normal bowel function [16].

A systematic review of FMT in IBS up to early 2017 identified 9 relevant publications (6 conference abstracts, 1 case report, 1 letter to the editor, 1 clinical review) that described a total of 118 patients [7]; in a pooled analysis of the results, after exclusion of data from reports that reported only short-term follow up or that did not provide diagnostic criteria or outcome data, 28 (58%) of the 48 remaining patients reported symptom improvement. However, there was no standardized outcome for these small, non-randomised, open-label studies and, for the 38 participants whose IBS was characterised, 20 (53%) had IBS-D, 16 (42%) had IBS-C and 2 (5%) had IBS-M.

In a single-centre, double-blind, RCT, 90 patients with IBS-D (47%) or IBS-M (53%) were assigned, in a 2:1 ratio to FMT or placebo, the FMT group being assigned 1:1 to *frozen* or *fresh* transplants [18]. After 3 months, symptom improvement (a decrease in the IBS-SSS score > 75) was reported by 63% (36/55) in the FMT group and by 43% (12/28) in the placebo group (p=0.049); however, after 12 months, there was no significant difference between the groups (FMT: 56% (31/55), Placebo: 36% (10/28); p=0.075). *Post hoc* analysis, after adjustment for comorbidities, showed no difference in outcomes when comparing fresh and frozen transplants [18]. Only one serious adverse event was reported in this study (transient vertigo and nausea after FMT requiring inpatient observation) with another 5 minor adverse events (2/57 in the FMT group, 3/30 in the placebo group) attributed to the medication and instrumentation used at colonoscopy (Figure 5).

A more recent multi-site study, published in abstract, reported no difference in outcomes for 48 patients with moderate-severe IBS-D (IBS-SSS $\geq$ 175) who were randomised 1:1

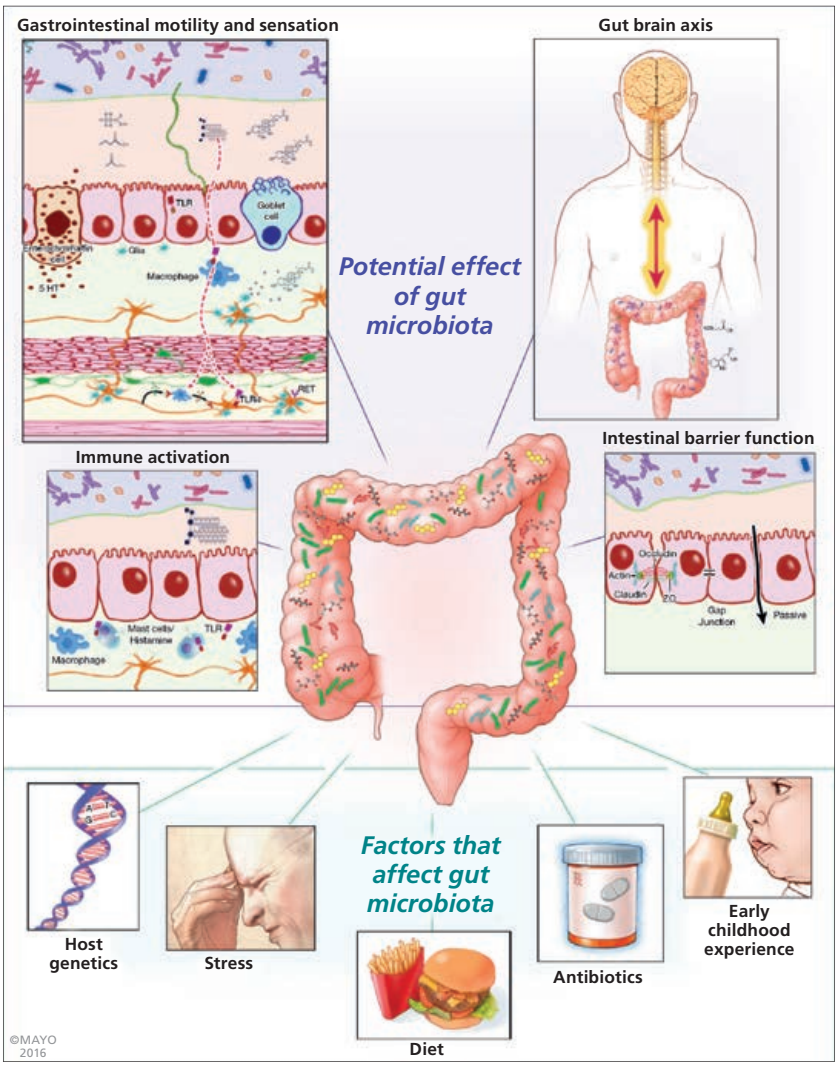


Figure 4: *A schematic diagram of factors that may affect the gut microbiota and the effects of the gut microbiota on a number of different host processes (from Battarai* et al. *[15])*

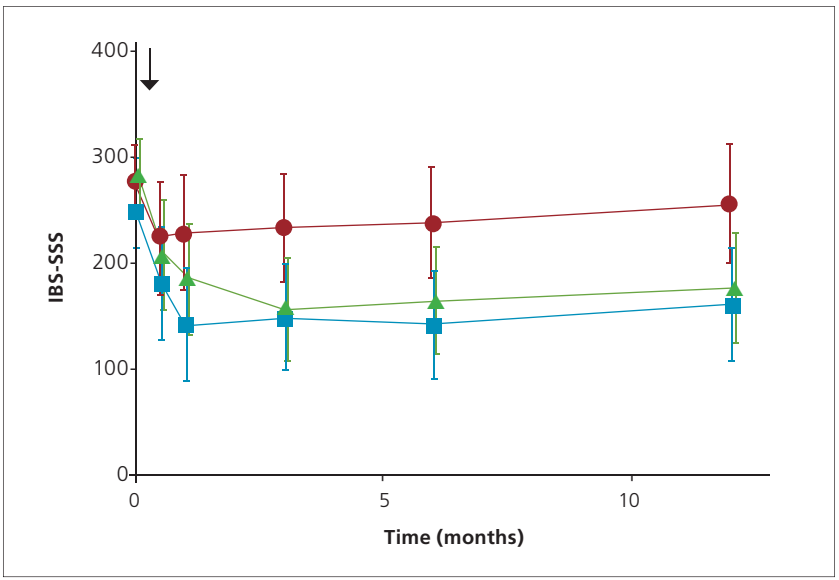


Figure 5: *A post hoc analysis of the effect of FMT for IBS on IBS symptom severity (IBS-SSS) comparing placebo, fresh stool and frozen stool transplants after adjustment of the IBS-SSS scores for other somatic functional comorbidities (from Johnsen* et al. *[18])*

to 25 FMT capsules daily for 3 days or placebo; at 12 weeks, a clinical response (a decrease in the IBS-SSS score >50) was reported by 48% in the FMT group compared with 63% in the placebo group (p=0.32).

There are, now, several randomized, double-blind, placebo-controlled trials in progress but the role of FMT for IBS in clinical practice is likely to remain unclear for the foreseeable future. Clearly, evidence-based guidance on FMT for IBS will require greater standardisation for the diagnosis of IBS and its subtypes as well as better characterisation of patient-relevant symptoms and their severity; it will also require a better understanding of the roles of the patient's diet, microbiome composition and immunological status and a more detailed characterisation and, possibly, personalization of the transplanted stool.

Metabolic Syndrome & Obesity

Metabolic syndrome, defined by the presence of 3 or more metabolic risk factors

including central obesity, high triglyceride levels, low HDL cholesterol levels, hypertension and high fasting blood sugar, has been associated with microbiome changes and microbiome-dependent changes in bile acid metabolism, epithelial permeability and immune function. A pilot, double-blind RCT, comparing allogenic FMT from a lean donor in 9 patients with autologous FMT in another 9 patients reported that allogenic, lean donor FMT was associated with increased insulin sensitivity, increased microbial diversity and increased short chain fatty acids (SCFA) after a 6-week course of treatment [20]. However, although a larger follow-up trial from the same group confirmed increased insulin sensitivity at 6 weeks in the allogenic lean donor FMT group (n=26), there were no longer any significant metabolic differences between the treatment groups at 18 weeks after FMT and the duodenal and fecal microbiota composition at 18 weeks after allogenic FMT was similar to baseline [21].

In summary, there is evidence that metabolic syndrome and obesity are associated with microbial profiles different from those of healthy, lean individuals and that lean donor FMT can produce metabolic and microbial changes, at least in the short-term. However, the sustainability of any FMT-related changes remains unclear and the long-term effects on the recipient microbiome and metabolic status are not known.

Hepatic Encephalopathy

Hepatic encephalopathy (HE), associated with increased mortality in late-stage cirrhosis, has been linked to significant intestinal dysbiosis with reduced abundance of potentially beneficial *Lachnospiraceae* and *Ruminococcaceae* familiies and an increased abundance of the pathogenic *Enterobacteriaceae* and *Streptococcaceae* [22]. In addition, the most commonly used therapies – e.g. lactulose, rifaximin – are presumed to work, in part at least, because of their effect on the microbiome. It seems reasonable, therefore, to hypothesise that modification of the microbiome in advanced cirrhosis will reduce HE severity. An initial case report reported resolution of HE in a 57-year old patient, accompanied by normalisation of his mental status and significant changes in his microbial composition after weekly FMT for 5 weeks [23]. A subsequent open-label RCT was conducted in 20 patients randomised 1:1 to FMT or *standard of care* therapy; FMT patients received broad spectrum antibiotics for the first 5 days, before being given an FMT enema on day 5; they could continue prior therapy with lactulose and rifaximin and they were, then, reassessed on days 6, 12, 20 and 35. FMT was well-tolerated and associated with fewer serious adverse events, reduced progression to further HE and improved cognition as well as increased microbiota diversity and greater numbers of beneficial taxa [24].

These are promising results, consistent with current understanding of the pathogenesis of HE, but the data are still scant and, despite the paucity of adverse events, much larger, randomised, controlled trials will be needed to determine whether FMT is appropriate for HE, particularly in view of the immune compromise associated with late-stage cirrhosis.

Anxiety & Depression

The improvement in HE after oral antibiotic therapy [22,25] is a clear indication that the gut microbiome affects brain function. There is, also, increasing evidence that anxiety and depression are associated strongly with the IBS and other functional gastrointestinal disorders (FGID) and severity of these neuropsychiatric conditions is related to the number of coexistent FGIDs and the frequency and severity of GI symptoms [26]. Studies in the mouse have shown that modification of the microbiota by oral, but not intraperitoneal, antibiotics led to an increase in exploratory activity and hippocampal expression of brain derived neurotropic factor (BDNF) and that colonization of germ-free BALB/c mice with microbiota from NIH Swiss mice increased exploratory behavior and hippocampal levels of BDNF, whereas colonization of germfree NIH Swiss mice with BALB/c microbiota reduced exploratory behavior [27].

There is increasing evidence that a bidirectional microbiota-gut-brain axis (Figure 6) is key to understanding the pathogenesis of a range of neuropsychiatric conditions and that modification of the gut microbiome may ameliorate, if not cure some of these conditions [28].

The demonstration that reciprocal microbiota transfer between different mouse strains was associated with reciprocal behavioural changes has been followed by studies showing that transfer of fecal microbiota from depressed patients to microbiota-depleted rats [29] or germ-free mice [30] led to the development of a depressive-related phenotype in the recipient animals and that transplantation of microbiota from patients with IBS and anxiety induced GI symptoms and anxiety-related behaviours in the recipient mice [31]. The finding that a probiotic, *Bifidobacterium longum* NCC3001, produced a reduction in depression scores in more IBS-D patients with anxiety or depression (14/22) than did placebo (7/22, p=0.04) and that the probiotic had a greater effect than placebo on central neural activity in the amygdala and frontolimbic regions provides further evidence that the gut microbiome affects anxiety and depression [32].

None of these studies has identified a specific pathogen or microbiota profile that is associated, reproducibly, with anxiety or depression; as for IBD and IBS, therefore, this raises the possibility that *normalisation* of the microbiome by FMT might ameliorate patients' anxiety or depression. A recent, open-label observational study in 17 patients with FGID, including IBS, functional diarrhea or functional constipation, reported that patients with a high depression score had lower microbial diversity and that FMT was associated with significant improvements in scores for depression, anxiety and sleep and in increase in microbial diversity, 4 weeks after the transplant [33].

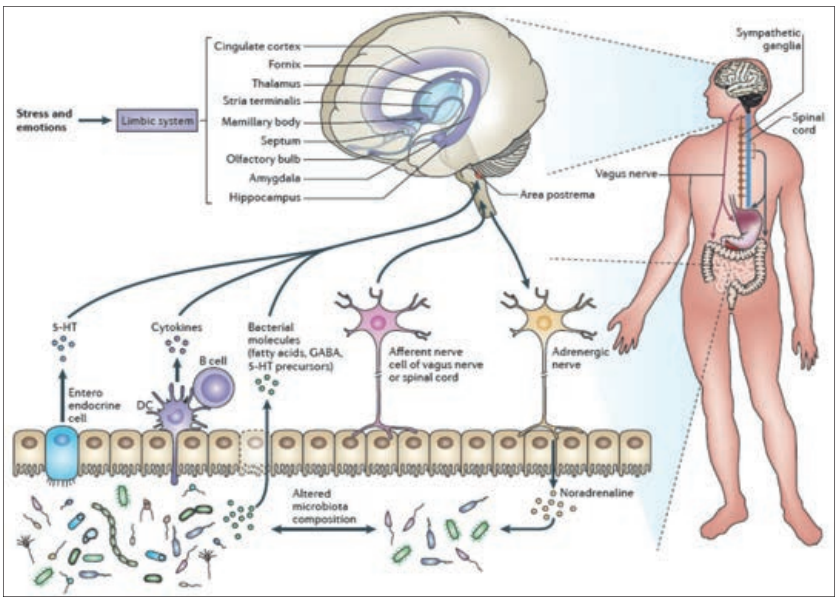


Figure 6: *The bidirectional microbiota-gut-brain axis. The neural, immunological, endocrine and metabolic pathways by which the microbiota influences the brain, and the proposed brain-to-microbiota component of this axis. Putative mechanisms by which bacteria access the brain and influence behaviour include bacterial products that gain access to the brain via the bloodstream and the area postrema, via cytokine release from mucosal immune cells, via the release of gut hormones such as 5-hydroxytryptamine (5-HT) from enteroendocrine cells, or via afferent neural pathways, including the vagus nerve. Stress and emotions can influence the microbial composition of the gut through the release of stress hormones or sympathetic neurotransmitters that influence gut physiology and alter the habitat of the microbiota. Alternatively, host stress hormones such as noradrenaline might influence bacterial gene expression or signaling between bacteria, and this might change the microbial composition and activity of the microbiota. DC, dendritic cell; GABA, γ-aminobutyric acid (from Collins* et al. *[28])*

Neuropsychiatric and Neurodevelopmental Disorders

There is an increasing number of studies and reviews evaluating the role of the gut microbiota in the pathogenesis of central nervous system disorders including age-related changes, Parkinson's disease, Alzheimer's disease, multiple sclerosis, stroke and brain injury, autism spectrum disorder (ASD), addiction behaviour, attention deficit hyperactivity disorder (ADHD) and schizophrenia; recent, detailed reviews have sum-

marised the findings in individuals with these disorders and highlighted numerous abnormalities or changes in gut microbiota or differences from the gut microbiota of normal individuals [34,35]. Currently, however, there is little evidence that the reported differences in gut microbiota are causally-related to the associated central neurological disorders.

The potential effect of the gut microbiome on autism or ASD has, perhaps, excited the most interest because many of these children have troublesome GI symptoms in the context of a condition for which the underlying cause is unknown and the treatment options are limited [34,36]. Based on the observation that regressive-onset autism had been associated with antibiotic exposure and subsequent diarrhea, an open-label trial of oral vancomycin was conducted in 10 children; unfortunately, initial behavioural improvements were not sustained [37]. More recently, an open-label study in 18 children with ASD reported that a 2 week-course of oral vancomycin followed by bowel cleansing and PPI therapy and, then, daily oral or weekly rectal microbiota transfer therapy for 7 to 8 weeks led to improvements in GI symptoms and behavioural ASD symptoms for at least 8 weeks after completion of the MTT. The authors reported partial engraftment of the donor microbiota and suggested that this could indicate long-term impact from this FMT regimen in ASD [38].

Exploratory, open-label studies are key to understanding the potential effects of complex interventions but larger, randomized controlled trials are essential before treatments such as FMT can be considered in clinical practice for conditions such as ASD or other complex neurological disorders.

The lower gastrointestinal tract contains almost 100 trillion micro-organisms, including more than 1000 bacterial species and this does not account for the presence and potential effects of different bacterial strains, viruses, bacteriophages, fungi and parasites [28]. In view of this and of the almost limitless complexities of the bidirectional microbiota-gut-brain axis with its ability to learn or adapt to prior environmental stimuli over the course of a lifetime, it is not at all surprising that associations will be discovered, serendipitously, between some features of the microbiota and the presence of some neurological or behavioural disorder.

Adverse Events

Adverse events of FMT may be due to the treatment itself or to the ancillary procedures such as colonoscopy, endoscopy or naso-enteric intubation. A recent overview identified 28 reports, including 3 RCTs, comprising 1089 and 1555 patients and concluded that the majority of adverse events were self-limited, mild gastrointestinal symptoms. Serious adverse events were observed, primarily in patients receiving FMT for CDI, including 3 deaths (0.25%), 3 cases of perforation and 4 cases of Gram-negative bacteremia [16]. The authors note that patients with recurrent CDI often have other

comorbidities that could have contributed to the increased risk of adverse events but it is important to note that there are no large studies in patients with IBD, IBS or other non-gastrointestinal studies and that most of these conditions do not confer the same risks of morbidity or mortality associated with recurrent CDI. In view of this, and of the very limited data on the long-term outcomes of FMT, it is too early to assume that FMT is safe or appropriate for routine clinical practice. Furthermore, FMT is a very complex intervention without many of the manufacturing, regulatory and approval safeguards that are present for pharmacological therapies; as a result, there is a clear need for guidelines on the many aspects of FMT, including indications, donor selection, FMT material preparation, clinical management and FMT delivery and the basic requirements for implementing an FMT centre such as those published by the European FMT Working Group [39] and the British Society of Gastroenterology with the Healthcare Infection Society [7].

Summary & Conclusions

Notwithstanding the success of FMT in patients with recurrent CDI, it is important to note that, in principle, CDI differs significantly from other dysbiosis-linked conditions in that the etiological agent has been identified for CDI whilst the pathogenesis is unknown or, even multifactorial, for almost all other dysbiosis-linked diseases or syndromes such as IBD, IBS, HE, metabolic syndrome and neuropsychiatric disorders. Until the pathogenesis of these other conditions has been better-defined, FMT and other techniques to modify the GI microbiome will remain speculative and investigational. In consequence, FMT, in particular, should be performed only in a research setting for the majority of dysbiosis-linked conditions [1] and, even, for patients being treated for CDI, the treatment and outcomes (short- and long-term) should be documented meticulously. A recent systematic review of published FMT studies concluded that many important methodological elements had not been reported with respect to donor eligibility criteria (47%), stool collection protocols (96%), stool preservation methods (76%) or microbiota composition (58%) [3]. Comprehensive, standardised documentation of study protocols, methods and outcomes is essential for all clinical trials but it is reasonable to hold FMT trials to an even higher standard in view of the need to interpret and replicate study findings in the context of a therapy that is almost impossible to standardize and has significant potential to cause harm which may not become evident for many years.

Recognition of the wide-ranging interactions between the human gastrointestinal microbiome and the host, as well as their mutual dependencies has led to tremendous interest and enthusiasm for investigating how modifications of the microbiome, whether by diet and prebiotics, probiotics, antibiotics or fecal microbiota transplantation, may affect a wide range of symptoms and diseases. However, there is a significant danger that the enthusiasm is, in many cases, uncritical or, even, misplaced and the potential risks of FMT, in particular, must be assessed as rigorously as the putative benefits.

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CURRENT AND FUTURE
MANAGEMENT OF DIGESTIVE
DISEASE: FROM BENCH TO BEDSIDE

Notes


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Notes

STRESA, November 8-10, 2018

VENUE: REGINA PALACE HOTEL

FLOOR PLAN
-1ST AND -2ND FLOOR