GI-MAP™ Interpretive Guide

Dr Oliver Frey, MD MRCGP

Private GP in Suffolk with special interest in Thyroid Health

© 2019 - www.CountryHealth.co.uk

Contents

About Dr Frey

Dr. Frey has dedicated his life to helping people take control of their health. His aim is to help his clients to learn how to become healthier, and take or regain control of their health.

Over 25 years of studying and practice in a variety of fields in medicine in Germany, England, Estonia and Switzerland give Dr Frey a fair bit of experience.

He first began treating patients in Germany in 1992 in cardio-thoracic surgery, followed by abdominal and vascular surgery, orthopaedics and trauma in state-run hospitals and a private hospital. In order to expand his skills he moved to the UK in 1997 where he spent three years training as a general medical practitioner, further specialising in diabetes care.

After several years, Dr. Frey took time out to reflect – moving to Estonia where he joined a spa hotel as strategic development director and chief physician. He became a life and health coach and was featured on Estonian TV. Dr Frey began exploring the fascinating field of functional medicine and developed screening tests and treatment packages for the hotel clients.

Soon he opened his first private practice, exploring a different way to offer healthcare. After modifying his patient's diet, he saw drastic – and often permanent – improvements in their health, this despite years of unsuccessful treatment by specialists.

After a short period in Switzerland as single-handed GP he moved back to England. In addition to his private work he supports an outstandingly rated NHS practice in Suffolk.

On his way he collected an MD "magna cum laude", membership of the Royal College of General Practitioners (MRCGP), a Diploma in Diabetes Care from Warwick, skills in acupuncture and neural therapy, and even life coaching, homeopathy, Reiki and EFT.

Dr Frey sees patients in his private practice in Ipswich. He has a special interest in thyroid health.

Contact details:

- www CountryHealth.co.uk
- Email reception@countryhealth.co.uk
- Practice tel: 01473 218 373

Introduction

Microbiology and DNA Analysis

In the last few decades, DNA analysis has transformed the field of microbiology. We become more and more aware of the health benefits or disease risks brought about by the microorganisms that inhabit the human body - the microbiome. Culture techniques, previously the standard, left up to 50% of bacterial species virtually invisible.

With DNA analysis we can now identify tremendous numbers of previously unknown organisms. Anaerobic bacteria make up a large part of the human microbiome and can be opportunistic and cause illness.

The Gastrointestinal Microbial Assay Plus (GI-MAP) was designed to assess a patient's microbiome from a single stool sample, with particular attention to microbes that may be disturbing normal microbial balance and may contribute to disorders in the gastrointestinal (GI) flora or illness.

The panel is a comprehensive collection of microbial targets as well as immune and digestive markers. It screens for pathogenic bacteria, commensal bacteria, opportunistic pathogens, fungi, viruses, and parasites.

The GI-MAP measures pathogenic organisms that can cause hospital-acquired infections (HAI) such as C. difficile or norovirus, foodborne illness such as E.coli or Salmonella, and common causes of diarrhea such as Campylobacter, Shigella, and rotavirus A.

This panel measures viral causes of gastroenteritis, unavailable by other common stool tests. It measures parasites such as Cryptosporidium, Giardia, and Entamoeba histolytica. The GI-MAP analyzes Helicobacter pylori and its virulence factors. It can detect opportunistic pathogens such as Pseudomonas aeruginosa, Klebsiella pneumoniae, Yersinia enterocolitica, and Proteus mirabilis, associated with autoimmune molecular mimicry.

It includes a panel of single-celled, amebic parasites such as Blastocystis hominis, Dientamoeba fragilis, and Entamoeba coli. Fungal organisms are measured by the GI-MAP such as Candida, Geotrichum, and Microsporidia, with the latter being a new addition to DNA stool analysis.

Finally, the GI-MAP measures standard markers of immunity, inflammation and digestion including calprotectin, secretory immunoglobulin A (sIgA), anti-gliadin antibody, and pancreatic elastase. [1]

Target Analytes

The human gastrointestinal microbiome houses trillions of bacteria and research shows that these microorganisms are essential for human metabolism[2], nutrition, immune function[3], and resistance to infection[4].

Over 500 different species of microorganisms from 30 different genera have been identified from the human gut. But in any one person, there are 100 million- 1 trillion microorganisms per gram of fecal content. Most microbes in the human gut are believed to be beneficial or commensal. There are microbes that colonize many people but only become pathogenic in certain situations (opportunistic pathogens). Finally, there are pathogens that are widely recognized to cause disease in the human host.

Although they are ubiquitous, pathogenic bacteria do not cause illness in all people. This is because commensal gastrointestinal flora can protect the host from infection. When gut microflora protects the intestines from pathogens and harmful microorganisms it is called, "colonization resistance."

Animal models show that when normal gut microflora are lacking, the host is more susceptible to GI infections with Salmonella. Similarly, after antibiotic treatment there is increased risk of pathogenic infections. On the other hand, commensal bacteria such as Lactobacillus and Bifidobacterium can prevent gastrointestinal infection.

Colonization resistance explains why most pathogenic bacteria fail to cause disease in healthy subjects [5]. Commensal bacteria naturally inhabit the human gastrointestinal tract and do not cause disease.

[1] Fasano A. Intestinal permeability and its regulation by zonulin: diagnostic and therapeutic implications. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2012;10(10):1096-1100

[2] Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. Nature. 2006;444(7122):1022-1023.

[3] Palva A. [Intestinal microorganisms and their significance for health]. Duodecim; laaketieteellinen aikakauskirja. 2009;125(6):685-694.

[4] Kamada N, Seo SU, Chen GY, Nunez G. Role of the gut microbiota in immunity and inflammatory disease. Nature reviews. Immunology. 2013;13(5):321-335

[5] Stecher B, Hardt WD. The role of microbiota in infectious disease. Trends in microbiology. 2008;16(3):107-114

Many are beneficial; they produce enzymes[6], vitamins[7], short chain fatty acids[8], and other metabolic products that keep the bowels and the body functioning well.

The incredibly complex interaction between human health and the gastrointestinal microbiome is the subject of multiple cutting-edge research studies. Given the metabolic, nutritional, and immune-enhancing roles of these organisms, the microbiome deserves close analysis when treating patients with chronic illness.

Pathogens

The GI-MAP measures bacterial pathogens such as Campylobacter, Escherichia coli (E. coli) O157, Enterotoxigenic E. coli, Shiga-like toxin-producing E.coli, Clostridium difficile, Salmonella, Shigella, and Vibrio cholerae.

The new GI-MAP qPCR technique was developed, verified, and validated with hundreds of specimens at Diagnostic Solutions Laboratory. It indicates if it the colonisation of specimens is high enough to cause pathology by medical standards. In one comprehensive review of rapid molecular technologies compared to conventional culture techniques, the authors concluded that there was sufficient evidence to recommend testing with PCR for Campylobacter, E. coli O157, and Salmonella and that it may yield better results than culture techniques[9] and is faster for pathogen identification, providing clinicians with a larger panel of pathogens, helping to contain nosocomial outbreaks before they spread[10].

Bacterial pathogens are often spread due to contamination of food and water with fecal material containing these pathogens. Antibiotic therapy is not always recommended because antibiotic resistance can worsen the infection. Hydration, probiotics, and supportive therapies for the gut-immune system can help to remove the pathogen from the GI tract.

The presence of a pathogen does not, by itself, indicate disease[11]. Results from laboratory tests must be interpreted together with clinical symptoms and history by a qualified health practitioner.

---

[6] Chow J. Probiotics and prebiotics: A brief overview. J Ren Nutr. 2002;12(2):76-86
[7] Ramakrishna BS. Role of the gut microbiota in human nutrition and metabolism. Journal of gastroenterology and hepatology. 2013;28 Suppl 4:9-17
[8] Hijova E, Chmelarova A. Short chain fatty acids and colonic health. Bratislavske lekarske listy. 2007;108(8):354-358
[9] Abubakar I, Irvine L, Aldus CF, et al. A systematic review of the clinical, public health and cost effectiveness of rapid diagnostic tests for the detection and identification of bacterial intestinal pathogens in faeces and food. Health Technol Assess. 2007;11(36):1-216
[10] Kahlau P, Malecki M, Schildgen V, et al. Utility of two novel multiplexing assays for the detection of gastrointestinal pathogens - a first experience. SpringerPlus. 2013;2(1):106
[11] xTAG gastrointestinal pathogen panel. Luminex http://www.luminexcorp.com/Products/Assays/ClinicalDiagnostics/xTAGGPP/. Accessed April 9, 2015

With increased awareness of the complexity of the GI environment, a pathogen is likely to cause disease if there are vulnerabilities in the host's defenses. For example, imbalanced microflora, poor immune defenses, poor diet, toxic exposures, antibiotics, or chronic GI symptoms could make a person more susceptible to harm from a pathogen, whereas another person may carry a fecal pathogen but is in good health.

In healthy patients, treating pathogens may not be necessary. However, continuing to support a beneficial and diverse microbiota and a strong gut-immune system will further protect the host from infection[12] [13].

Populations of microorganisms can change dramatically in short periods of time, especially under stress, with the use of antimicrobial medications, or changes in the diet, etc. The transient nature of gastrointestinal microorganisms makes it even more important to use the lab results together with signs and symptoms to determine if a particular lab finding is indicative of a clinical condition that requires treatment.

Clinical monitoring and follow-up testing and confirmation by other testing methods helps to analyze the changes to the microbiome over time and verify clinically relevant findings. A pathogenic organism finding on a test result does not necessarily indicate treatment, even when there are symptoms of disease. Healthy, immune-competent people can naturally eradicate a pathogen with basic healthcare practices and the passage of a few weeks, making treatment unnecessary.

Clostridium difficile (C. difficile or C. diff)

This is a well-known pathogen that can cause colitis and Clostridium difficile-associated diarrhea or CDAD. It commonly presents with mild to moderate diarrhea and occasionally abdominal cramping. C. diff is able to colonize the GI tract after a disturbance of the microbiota, generally after antibiotic therapy. C. diff releases toxins that cause inflammation and damage to the GI lining. It infects nearly 20% of hospitalized patients, making it the most common nosocomial infection.

Toxins A and B are the major virulence factors believed to be responsible for C. diff infection symptoms. They are proinflammatory and cytotoxic. They damage the cytoskeleton of intestinal epithelial cells, permitting fluid influx, they open tight junctions in the GI lining, and thereby damage the GI lining. Toxins A and B have even shown systemic effects in animal models, suggesting that their bioactivity may not be localized to the GI tract.

---

[12] Palva A. [Intestinal microorganisms and their significance for health]. Duodecim; laaketieteellinen aikakauskirja. 2009;125(6):685-694

[13] Fukushima Y, Kawata Y, Hara H, Terada A, Mitsuoka T. Effect of a probiotic formula on intestinal immunoglobulin A production in healthy children. International journal of food microbiology. 1998;42(1-2):39-44

Escherichia coli

This is a large and varied species of bacteria that includes many strains. They colonize humans and animals and are spread through contaminated water, food, or contact with infected humans or animals. E. coli can cause infections outside of the GI tract such as urinary tract infections, meningitis, and intra-abdominal abscess.

While there are many harmless, and even beneficial, E.coli strains, there are six strains that are notorious for their pathogenicity, especially for GI infections:

- Enterotoxigenic E. coli (ETEC) can cause traveler's diarrhea
- Enteropathogenic E. coli is a cause of childhood diarrhea
- Enteroinvasive E. coli (EIEC) can lead to dysentery similar to that caused by Shigella.
- Enterohemorrhagic E. coli can lead to hemorrhagic colitis or hemolytic-uremic syndrome.

EIEC and EHEC colonize the colon while the others colonize the small intestines and subsequently initiate diarrhea.

The serotype O157:H7 has been implicated in many outbreaks and cases of bloody diarrhea and hemolytic uremic syndrome and has a high prevalence worldwide.

Enterotoxigenic E. coli heat-labile toxin (LT) and heat-stable toxin (ST) are the enterotoxins responsible for diarrheal disease in humans. ST-producing E.coli is widely known to cause diarrhea but the mechanism is still unknown. LT acts similarly to the cholera toxin by activating adenylate cyclase, leading to diarrhea.

Shiga-like toxin producing E.coli (STEC) has been involved in foodborne illness outbreaks. It causes various GI illnesses, including bloody and non-bloody diarrhea. Shiga toxin (stx1) and Shiga toxin 2 (stx2) are generally considered to be the virulent factors responsible for serious illness caused by STEC. Stx1 and Stx2 are genetic targets that help accurately detect the presence of Shiga-like toxin producing E.coli in stool samples.

Salmonella

is the most common cause of foodborne illness, affecting 1.2 million Americans each year. 19,000 people are hospitalized and 400 people die from Salmonella each year in the U.S. It is the largest health burden of all the bacterial pathogens. Salmonella enterica and Salmonella bongori make up this genus. Salmonella species typically cause gastroenteritis with fever, vomiting, and severe diarrhea. It usually resolves within one week. Systemic infections may occur and require antibiotic

interventions. A few serotypes, such as S. Typhi, cause enteric fever which is characterized by a high fever, abdominal pain, and malaise, without diarrhea or vomiting.

Salmonellosis often follows consumption of contaminated food or water. The number of Salmonella cells needed to produce disease varies widely, suggesting that even small amounts can initiate illness. As little as 10 cells (in contaminated food) can trigger illness, all the way up to 105 to 106 cells (based on clinical studies. Food sources include:

- Poultry
- Poultry products
- Meat
- Dairy
- Raw, fresh, ready-to-eat produce
- Tomatoes
- Melons
- Leafy greens
- Sprouts
- Berries

Treatment

Because salmonella infection can be dehydrating, treatment focuses on replacing fluids and electrolytes. Severe cases may require hospitalization and fluids delivered directly into a vein (intravenous). In addition, your doctor may recommend:

- Anti-diarrheals. Medications such as loperamide (Imodium A-D) can help relieve cramping, but they may also prolong the diarrhea associated with salmonella infection.
- Antibiotics. If your doctor suspects that salmonella bacteria have entered your bloodstream, or if you have a severe case or a compromised immune system, he or she may prescribe antibiotics to kill the bacteria. Antibiotics are not of benefit in uncomplicated cases. In fact, antibiotics may prolong the period in which you carry the bacteria and can infect others, and they can increase your risk of relapse.

Use oil of oregano for its antimicrobial properties can be helpful. The active ingredients found in essential oil of oregano include phenol, which is known for being able to destroy the bacteria-causing salmonella poisoning. [14]

Yersinia enterocolitica

This pathogen has been linked to food poisoning. It is also believed to be an autoimmune trigger.

---

[14] https://www.hi-tm.com/Documents/Spices.html

Parasitic Pathogens

A parasite is an organism that lives and feeds on a host organism at the expense of the host. Some parasites can cause infectious disease in humans but others do not. Parasites can live inside the gut, removing vital nutrients, and damaging the gut lining.

Some parasitic infections are easily treated and others are not, with symptoms ranging from mild discomfort to severe problems, including death.

It is commonly thought that parasitic infections occur mostly in underdeveloped countries, but these infections also affect people in developed countries including the United States. In fact, such pathogens can survive in their hosts and cause health problems that may be hard to identify.

Parasitic pathogens that infect the gastrointestinal tract typically cause a wide variety of symptoms such as diarrhea, constipation, abdominal cramping, bloating, gas, nausea, and vomiting. In immunosuppressed patients, symptoms may involve the central nervous system.

Contaminated food and drinking water present the highest risk for parasite transmission, but lakes, swimming pools, and sexual contact are also ways a person can contract these pathogens. The fecal-oral route is a common way that parasitic pathogens are spread. Therefore, poor hygiene or any conceivable contact with fecal material could result in parasitic infection.

Treatments should be specific and based on the type of parasite identified. Efforts should be made to interrupt the parasite's life cycle to prevent reinfection. Once symptoms are gone, it is important to retest to make sure the parasite has been eradicated.

Cryptosporidium

This parasite is notorious for being spread by swimming pools. Cryptosporidium can cause gas, bloating, diarrhea, and abdominal pain. In a healthy, immune-competent person, this is a self limiting infection and can be cleared within 2-3 weeks.

Entamoeba histolytica (E. histolytica)

This is a disease-causing parasite that can affect anyone, although it is more common in those who lived or travelled in tropical areas with poor sanitary conditions. Diagnosis can be difficult since, under a microscope, it looks similar to other parasites such as Entamoeba dispar and Entamoeba hartmanii. The latter two parasites generally do not cause illness.

E. histolytica is transmitted via the oral-fecal route or from contaminated food or surfaces. Infected people do not always become sick and symptoms are often mild including stomach cramps and loose stools. This parasite can infect the liver or spread to other parts of the body including the lungs and brain, although this is not as common.

Research has shown that in a small percentage of patients with amebic liver abscess, the infection can cause brain abscess with the patient presenting with central nervous system symptoms.

Treatment for infection with E. histolytica includes antiparasitic drug therapy and may include a combination based on the severity of infection.

Giardia intestinalis

Previously called Giardia lamblia, this is the most commonly identified intestinal parasite in the United States and the most commonly isolated protozoan worldwide. It may be asymptomatic or it can cause chronic diarrhea. It is found in outside water sources such as lakes, streams, and ponds, and it can also get past filtration systems. It is possible for as little as 10 cysts to cause infection.

Animals carry Giardia and it is common in daycare workers and institutionalized patients. Giardia can cause significant symptoms in people with malnutrition, immunosuppression, or cystic fibrosis. Travelers, immunocompromised patients, and certain sexually active homosexual men have high risk for developing giardiasis.

Giardia can cause:
- Diarrhea (90%)
- Fatigue
- Abdominal distention and cramps (70-75%)
- Gas
- Nausea and vomiting
- Foul-smelling, greasy stools
- Anorexia
- Weight loss (66%)
- Neurologic symptoms such as irritability, sleep disorder, depression, neurasthenia
- Urticaria
- Malnutrition
- Growth retardation in children

Metronidazole and tinidazole are approved pharmaceutical treatments for giardiasis.

Viral Pathogens

Adenovirus, norovirus, and rotavirus are viral causes of gastroenteritis that are normally self-limiting in healthy individuals. When a clinician is looking for a microbial cause of gastroenteritis, they would be remiss to overlook these viruses as possible causes of diarrhea, abdominal pain, and vomiting.

In a study of 4,627 patients with gastroenteritis, PCR stool technology detected norovirus in 36% and rotavirus A in 31% of samples. Another study of over 300 people with acute diarrhea over the course of a year showed 36.0% were positive for norovirus and 17.3% were positive for rotavirus, while 5.4% were positive for adenovirus. In total, viruses accounted for 58.7% of cases of acute gastroenteritis, pointing to the value of viral detection in stool.

Norovirus can be detectable for over three years in groundwater and infectious for at least 61 days[15]. There are no standard treatments for viral gastroenteritis in healthy hosts. Antivirals are not recommended. Supportive care for the gastric mucosa, hydration, and immune-boosting agents may be warranted.

Adenoviruses 40 and 41

Both can cause gastroenteritis. They are a common cause of diarrhea in infants and children but can also affect adults. These pathogens can replicate readily in the intestine. They are the only adenovirus types that are shown to be causative agents of gastrointestinal disease. However other adenoviruses may cause gastroenteritis. Fever and watery diarrhea are usually limited to 1-2 weeks. Adenoviruses 40 and 41 may also be present in the stool of asymptomatic carriers and may not require treatment[16].

Adenoviruses 40 and 41 belong to the larger group of adenoviruses, including 52 different serotypes, known to cause a variety of illnesses from respiratory tract infections (common cold, sore throat, bronchitis, pneumonia) to bladder infection and cystitis. They are hardy viruses that are transmitted through close contact such as touching an infected person or surface, then shaking hands or touching your eyes, nose or mouth.

Other routes of transmission include blood, air particles (coughing or sneezing) and the oral-fecal route. Adenoviruses rarely cause severe illness, but infants and those with weakened immune systems have a higher risk of developing a more serious illness from the infection.

---

[15] Seitz SR, Leon JS, Schwab KJ, et al. Norovirus infectivity in humans and persistence in water. Applied and environmental microbiology. 2011;77(19):6884-6888.
[16] Gompf SG, Cunha BA. Adenoviruses clinical presentation. Drugs & Diseases 2014; http://emedicine.medscape.com/article/211738-clinical. Accessed May 19, 2015

Norovirus

This virus is the most common cause of nonbacterial gastroenteritis in the world. It is widely known for causing the stomach flu on cruise ships[17]. Three genotypes of this diverse virus, GI, GII, and GIV, can infect humans.

Norovirus, which can have a sudden or gradual onset, typically develops 24-48 hours after contact with an infected person or ingestion of contaminated food or water. Symptoms include nausea and vomiting, diarrhea, abdominal cramps, low grade fever, muscle aches, fatigue, and headache.

Norovirus is generally short-lived, lasting about 24-72 hours but it is highly contagious due to its stability in the environment and resistance to heat, cold, and disinfectant solutions. It can survive on hard surfaces for weeks and up to 12 days on contaminated fabrics.

Infection affects the microvilli of the small intestine, not the colon. Those infected can shed the virus for up to two weeks after recovery, continuing to spread the virus.

Noroviruses are the most common cause of sporadic diarrhea in community settings and cause up to half of all outbreaks of gastroenteritis.

Treatments for norovirus include hydration and electrolytes primarily, and in some cases antiemetics for nausea and vomiting, and analgesics for pain and headache. Intravenous fluid and electrolytes may be needed in extreme cases.

Helicobacter pylori

H. pylori and seven virulence genes are included on the GI-MAP. Helicobacter pylori has been evolving with human beings for well over 50,000 years, since they migrated out of Africa. H. pylori colonization has been implicated in a variety of gastroduodenal diseases including gastritis, gastric cancer, and duodenal and peptic ulcer[18].

H. pylori has also been detected by stool PCR in cases of dyspepsia, abdominal pain, and chronic gastrointestinal symptoms. It is infamous for its causal link to ulcers and gastric cancer, which resulted in a Nobel prize awarded to Robin Warren and Barry Marshall in 2005.

---

[17] Benaroch R. Norovirus: symptoms and treatment. WebMD 2012; http://www.webmd.com/children/norovirus-symptoms-and-treatment?page=2. Accessed 6/3/2015, 2015.

[18] Abadi AT, Taghvaei T, Wolfram L, Kusters JG. Infection with Helicobacter pylori strains lacking dupA is associated with an increased risk of gastric ulcer and gastric cancer development. Journal of medical microbiology. 2012;61(Pt 1):23-30.

H. pylori may protect its host from certain atopic disorders[19] as well as other diseases such as esophageal cancer[20], reflux, and obesity[21].

H.pylori genotyping may be useful for resistant H. pylori infections that have failed to respond to triple antibiotic therapy[22].

H. pylori is associated with high rates of cancer in certain regions, but not in others. Fifty percent of the world's population is believed to be infected with H. pylori but only 2% of those develop gastric cancer.

H. pylori may be asymptomatic and require no treatment or only supportive care to improve the intestinal mucosa and gastrointestinal lining. H. pylori may cause hypochlorhydria or hyperchlorhydria. Positive virulence genes represent the potential for an H. pylori strain to create pathology. Information about the potential for virulence may help the clinician determine if H. pylori treatment is necessary.

[19] Walker MM, Talley NJ. Review article: bacteria and pathogenesis of disease in the upper gastrointestinal tract--beyond the era of Helicobacter pylori. Alimentary pharmacology & therapeutics. 2014;39(8):767-779
[20] Thrift AP, Pandeya N, Smith KJ, et al. Helicobacter pylori infection and the risks of Barrett's oesophagus: a population-based case-control study. Int J Cancer. 2012;130(10):2407-2416
[21] Walker MM, Talley NJ. Review article: bacteria and pathogenesis of disease in the upper gastrointestinal tract--beyond the era of Helicobacter pylori. Alimentary pharmacology & therapeutics. 2014;39(8):767-779
[22] Schabereiter-Gurtner C, Hirschl AM, Dragosics B, et al. Novel real-time PCR assay for detection of Helicobacter pylori infection and simultaneous clarithromycin susceptibility testing of stool and biopsy specimens. Journal of clinical microbiology. 2004;42(10):4512-4518

Virulence Factors

BabA

(Blood group antigen binding adhesin) is an outer membrane adhesin protein that facilitates binding of H. pylori to the gastric mucosa. BabA is thought to play a significant role in inducing inflammation in the gastric mucosa and in promoting long-term infection. Higher expression levels of BabA are associated with severity of inflammation and the development of clinical disease[23].

CagA

(Cytotoxin-associated protein A) presence in H.pylori strains has been significantly associated with gastric cancer and peptic ulcer[24]. The gene codes for a type IV secretion system which allows the bacterium to inject the cagA protein into the host cell. Once inside the host's gastric epithelial cells, cagA can disrupt cell signaling, leading to abnormal proliferation, motility, and changes in the cytoskeleton. These changes to normal cell signaling can initiate cancer.

Cag PAI

The presence of CagPAI is associated with highly virulent strains of H. pylori[25].

DupA

(Duodenal ulcer-promoting gene A) is strongly linked to an increased risk for developing duodenal ulcers, but not gastric cancer. DupA is thought to be involved in inducing the inflammatory cytokine IL-8, as well as secretion of urease and inhibition of mitochondria-mediated apoptosis. However, the function of the DupA protein has not yet been well-established[26].

---

[23] Ansari S, Yamaoka Y. Helicobacter pylori BabA in adaptation for gastric colonization. World J Gastroenterol. 2017;23(23):4158-4169.
[24] Basso D, Zambon CF, Letley DP, et al. Clinical relevance of Helicobacter pylori cagA and vacA gene polymorphisms. Gastroenterology. 2008;135(1):91-99
[25] Naumann M, Sokolova O, Tegtmeyer N, Backert S. Helicobacter pylori: A Paradigm Pathogen for Subverting Host Cell Signal Transmission. Trends in microbiology. 2017;25(4):316-328
[26] Talebi Bezmin Abadi A, Perez-Perez G. Role of dupA in virulence of Helicobacter pylori. World J Gastroenterol. 2016;22(46):10118-10123.

IceA

(Induced by Contact with Epithelium A) has been linked to increased expression of the inflammatory cytokine IL-8, and the development of gastric inflammation, peptic ulcer disease, and gastric cancer, in some studies. However, the function of the IceA protein has not yet been established.

OipA

(Outer Inflammatory Protein A) is an adhesin protein found in the outer cell membrane of H. pylori, and functions in adherence of H. pylori to gastrointestinal mucosa. OipA contributes to the activity of the CagA virulence factor, and to H. pylori's ability to induce inflammation via IL-8. It is associated with gastric cancer and peptic ulcers[27].

Vacuolating toxin (vacA)

This virulence factor has been associated with gastric cancer, peptic ulcer, and duodenal ulcer[28]. The vacA gene is present in all strains of H.pylori but is polymorphic, which leads to different levels of vacuolating toxin. VacA toxins interact with certain receptors on host cells, setting off a chain of events including mitochondrial damage, inhibition of T-lymphocytes, and interference of antigen presentation.

NORMAL/ COMMENSAL BACTERIA

Trillions of microorganisms inhabit the human intestine to make up a complex ecosystem that plays an important role in human health. The gut microbiota is diverse, varies among individuals, and can change over time, especially during developmental stages and with disease. The predominant classes of bacteria in the gut are Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria.

The fungi that are part of the gut flora include Candida, Saccharomyces, Aspergillus, and Penicillum. These commensal (friendly) bacteria coexist with their human host and perform many important functions. They extract nutrients and energy from our diets, maintain gut barrier function, produce vitamins (biotin and vitamin K), and protect against colonization by potential pathogens[29].

---

[27] Horridge DN, Begley AA, Kim J, Aravindan N, Fan K, Forsyth MH. Outer inflammatory protein a (OipA) of Helicobacter pylori is regulated by host cell contact and mediates CagA translocation and interleukin-8 response only in the presence of a functional cag pathogenicity island type IV secretion system. Pathogens and disease. 2017;75(8)

[28] Basso D, Zambon CF, Letley DP, et al. Clinical relevance of Helicobacter pylori cagA and vacA gene polymorphisms. Gastroenterology. 2008;135(1):91-99.

[29] Kamada N, Seo SU, Chen GY, Nunez G. Role of the gut microbiota in immunity and inflammatory disease. Nature reviews. Immunology. 2013;13(5):321-335

Research has demonstrated the microbiota's capacity to interact with the immune system as an important health benefit[30]. The microbiota also has anti-inflammatory and antioxidant activity[31].

It is essential that commensal bacteria are diverse and balanced since disruption to the normal balance (or dysbiosis) has been associated with obesity, malnutrition, inflammatory bowel and other autoimmune diseases, neurological disorders, and cancer[32].

A limited list of commensal flora is included in the GI-MAP test as a general screen for levels of normal, protective flora or to monitor probiotic supplementation. These include Bacteroides fragilis, Lactobacillus and Bifidobacteria as well as E. coli.

Bacteroides fragilis

This is a human commensal bacterium that colonizes the lower gastrointestinal tract in mammals. Bacteroides species are some of the first microorganisms to colonize the human gut and are present in high numbers. B.fragilis is a very common, important, Gram-negative anaerobe yet it accounts for only approximately 0.5% of the Bacteroides species found in the gut. In its usual role as a commensal gut bacterium, B. fragilis has beneficial, immunomodulatory activity. However, if B. fragilis enters the bloodstream, as a result of intestinal permeability, trauma or surgery, it can cause serious infections[33].

B. fragilis has been the subject of rigorous investigation in recent years because it appears to have a protective effect against inflammation and possibly against autoimmune disorders. B. fragilis repairs defects in the gut barrier by influencing tight junction proteins and cytokine expression[34].

When autistic like mice were given Bacteroides fragilis, it normalized intestinal permeability, restored microbial balance, and removed behavioral and cognitive symptoms. B. fragilis has also been shown to correct gastrointestinal pathology in animal models of colitis[35] and inhibit neuroinflammation in mouse models of multiple sclerosis[36].

---

[30] Martin R, Miquel S, Ulmer J, Kechaou N, Langella P, Bermudez-Humaran LG. Role of commensal and probiotic bacteria in human health: a focus on inflammatory bowel disease. Microbial cell factories. 2013;12:71

[31] Khanna S, Tosh PK. A clinician's primer on the role of the microbiome in human health and disease. Mayo Clinic proceedings. 2014;89(1):107-114.

[32] Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. Nature. 2012;489(7415):220-230

[33] Maier E, Anderson RC, Roy NC. Understanding how commensal obligate anaerobic bacteria regulate immune functions in the large intestine. Nutrients. 2014;7(1):45-73

[34] Chow J. Probiotics and prebiotics: A brief overview. J Ren Nutr. 2002;12(2):76-86.

[35] D'Souza DH, Sair A, Williams K, et al. Persistence of caliciviruses on environmental surfaces and their transfer to food. International journal of food microbiology. 2006;108(1):84-91

[36] Atmar RL, Estes MK. The epidemiologic and clinical importance of norovirus infection. Gastroenterology clinics of North America. 2006;35(2):275-290, viii

Its anti-inflammatory activity is attributed to a surface molecule called polysaccharide A which promotes regulatory T cells and anti-inflammatory cytokines through toll-like receptor 2 (TLR2) signaling[37].

Bifidobacteria and Lactobacillus

Both are a natural part of the flora in the human body. They are often described as beneficial or commensal bacteria. They are given therapeutically as probiotics. These beneficial bacteria promote good digestion, regularity, boost the immune system[38], and help control intestinal pH. Bifidobacteria and Lactobacillus help prevent the overgrowth of Candida albicans, E. coli, and other pathogenic bacteria[39] [40].

Clostridium spp.

Clostridium is a genus of bacteria that includes over one hundred distinct species, many of which are abundant and normal inhabitants (commensal) of the human gastrointestinal tract (GIT). Clostridia are anaerobic gram-positive bacteria that produce very durable spores as a means of proliferation; the spores are extremely resistance to antibiotics, heat, drying and disinfectants. Clostridium has pathogenic and non-pathogenic species.

Most of the Clostridium species are not virulent and can even have beneficial effects on health and integrity of the GIT in part by breakdown of polysaccharides and fermentation of carbohydrates to short chain fatty acids. They are reported under the category of commensal.

However a few species are well-established opportunistic pathogens that produce specific toxins that cause diseases such as food-borne illnesses and, antibiotic-associated diarrhea and pseudomembranous colitis. Some species of Clostridium have been associated with neurological disorders and are the subject of ongoing research. They are listed under the Pathogen Section of the report.

---

[37] Maier E, Anderson RC, Roy NC. Understanding how commensal obligate anaerobic bacteria regulate immune functions in the large intestine. Nutrients. 2014;7(1):45-73.
[38] Sjogren YM, Tomicic S, Lundberg A, et al. Influence of early gut microbiota on the maturation of childhood mucosal and systemic immune responses. Clin Exp Allergy. 2009;39(12):1842-1851
[39] Stecher B, Hardt WD. The role of microbiota in infectious disease. Trends in microbiology. 2008;16(3):107-114
[40] Sheil B, Shanahan F, O'Mahony L. Probiotic effects on inflammatory bowel disease. J Nutr. 2007;137(3 Suppl 2):819S-824S

Clostridium Species and Autism

A hypothesis was presented that repeated antibiotic use in children might cause bacterial imbalance in the gastrointestinal tract (GIT) such that beneficial and, nonpathogenic commensal bacteria have been consequently diminished and replaced by one or more toxin producing species[41].

Clostridium species that produce neurotoxins and potentially toxic metabolic byproducts have been reported to be more prevalent in autistic children compared to neurotypical controls; most notable were greater quantities C. bolteae and members of the C. hystolyticum group.

Support for a connection between toxin producing bacteria in the GIT and autistic behavioral abnormalities and gastrointestinal symptoms was provided from a study in which a select sub-group of "regressive-onset" autistic children exhibited transient yet significant improvements while taking a minimally absorbed antibiotic.

However the gains attained were lost about two weeks after cessation of antimicrobial therapy. The rebound in symptoms may relate to the fact that the antibiotic does not kill the spores produced by Clostridium species and recolonization by the toxin-producing bacteria likely occurred.

The aforementioned Clostridium species produce not only species-specific neurotoxins but also toxic metabolic byproducts. By proteolytic fermentation they produce metabolites in the GIT such as ammonia, amines, volatile phenols, and indoles, which are toxic and present at only low levels in the normal GIT.

The amines produced by proteolytic Clostridium species include histamine, cadaverene, thymine and putrescene, which are pharmacologically active and can affect a variety of physiological functions.

Further reading:

- Sandler RH, Finegold SM, Bolte ER et al. Short-term benefit from oral vancomycin treatment of regressive-onset autism. J Child Neurol (2000)15:429-35.
- Song Y, Liu C and Finegold M. Real-time PCR quantitation of Clostridia in feces of autistic children. Appl Environ Microbiol (2004)70:6459-65.
- Parracho HMRT, Bingham MO, Gibson GR et al. Differences between the gut microflora of children with autistic spectrum disorders and that of healthy children. J Med Microbiol (2005)54:987-91.

---

[41] Bolte ER. Autism and Clostridium tetani. Medical Hypotheses (1998)51:133-44.

Enterobacter spp.

This is a Gram-negative genus in the Proteobacteria phylum and is closely related to E. coli (in the same taxonomic family). High levels may indicate increased intestinal inflammatory activity. Low levels may indicate reduced mucosal health.

Phyla Microbiota

Gram-negative Bacteroidetes and gram-positive Firmicutes are bacterial phyla that dominate the entire human digestive tract, including the mouth, nose, throat, and colon[42].

The amounts of Bacteroidetes and Firmicutes bacteria have been used by scientists to characterize gastrointestinal bacterial composition. Research over the last twenty years shows that human gut microbiota are involved in energy harvest and storage[43], lending them the nickname, "fat bugs."

Studies showed a characteristically high ratio of Firmicutes to Bacteroidetes (F/B ratio) in obese subjects when compared to lean subjects[44].

When obese subjects lost weight, there was a simultaneous change in the Firmicutes to Bacteroidetes ratio, favoring that of lean subjects[45].

Overall, it seems clear that there is GI microbial imbalance in people with obesity and this could be a modifiable factor for patients with metabolic disorders. Diet is one of the most powerful modulators of the GI microbiome. A high fat diet is a driver of microbial changes and can increase the F/B ratio.

Patients with a **high F/B ratio** may benefit from a lower fat diet and probiotics and prebiotics aimed to balance the Firmicutes and Bacteroidetes phyla. In one study, 30 grams of glutamine taken orally every day for two weeks lowered the F/B ratio[46].

---

[42] Segata N, Haake SK, Mannon P, et al. Composition of the adult digestive tract bacterial microbiome based on seven mouth surfaces, tonsils, throat and stool samples. Genome Biol. 2012;13(6):R42
[43] Xiao L, Sonne SB, Feng Q, et al. High-fat feeding rather than obesity drives taxonomical and functional changes in the gut microbiota in mice. Microbiome. 2017;5(1):43
[44] Armougom F, Raoult D. Use of pyrosequencing and DNA barcodes to monitor variations in Firmicutes and Bacteroidetes communities in the gut microbiota of obese humans. BMC genomics. 2008;9:576
[45] Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. Nature. 2006;444(7122):1022-1023
[46] de Souza AZ, Zambom AZ, Abboud KY, et al. Oral supplementation with L-glutamine alters gut microbiota of obese and overweight adults: A pilot study. Nutrition. 2015;31(6):884-889

Therapeutic Options for Abnormally Low Commensal Bacterial Findings

To improve the microbiome, the use a broad-spectrum, diverse probiotic formula, 50–450 billion CFUs/day which contains Lactobacillus acidophilus, Bifidobacterium bifidum, Bifidobacterium longum, Lactobacillus rhamnosus, Bifidobacterium breve, Lactobacillus casei, Streptococcus thermophilus might be useful.

The dietary intake of vegetables and fibers (psyllium, oat bran) should be increased and dietary sugar and refined carbohydrates should be reduced.

Prebiotic supplementation (resistant starch, xylooligosaccharide, inulin, beta-glucan, arabinogalactan) and fermented foods, if tolerated, can be helpful.

Opportunistic Bacteria or Overgrowth Bacteria

The GI-MAP was designed to detect pathogenic and opportunistic organisms that may be causing symptoms or illness. Many bacteria measured on the GI-MAP are opportunistic pathogens, meaning that they only cause disease and illness in some individuals, particularly the immune-compromised.

Many people come into contact with opportunistic pathogens and experience no symptoms, probably because opportunists are suppressed by the balance of commensal bacteria.

Overgrowth and excessive colonization by opportunistic bacteria may occur when the commensal bacteria are impaired by poor diet, antibiotic use, parasitic infection, or a weakened immune system. Opportunistic pathogens are not recognized by standard medical authorities to cause illness, and finding measurable quantities in the stool may be considered clinically insignificant. Examples are Citrobacter species or Morganella species.

However, certain opportunistic pathogens may be recognized in the integrative and functional medical field as creating imbalance in the gut microbiota or otherwise preventing proper healing of the GI mucosal barrier. Some of these organisms have been implicated in contributing to extraintestinal disease.

Pseudomonas species are gram-negative bacteria found widely in the environment. Pseudomonas aeruginosa is the most common species causing infection and can affect every portion of the intestine. In the gastrointestinal tract it can cause inflammation, epithelial barrier dysfunction, tight cell junction interruption, and intestinal permeability[47].

This bacterium exhibits enhanced virulence with stress, trauma, surgery, and cancer. Symptoms of enteric infection include fever, dehydration, abdominal distention, diarrhea, and physical findings of Shanghai fever[48]. The infection usually affects young children and adults with hematologic malignancies and neutropenia.

Outside the GI tract, it can cause urinary tract infections, dermatitis, bacteremia, bone and joint, respiratory, and systemic infections especially in immunocompromised individuals.

---

[47] Markou P, Apidianakis Y. Pathogenesis of intestinal Pseudomonas aeruginosa infection in patients with cancer. Frontiers in cellular and infection microbiology. 2014;3:115
[48] Chuang CH, Wang YH, Chang HJ, et al. Shanghai fever: a distinct Pseudomonas aeruginosa enteric disease. Gut. 2014;63(5):736-743

Bacillus spp.	Common group of gram-positive bacteria in the *Firmicutes* phylum. Some strains are used as probiotics. High levels may result from reduced digestive function, SIBO, or constipation.
Enterococcus faecalis *Enterococcus faecium*	Gram-positive species in the *Firmicutes* phylum. High levels may result from reduced stomach acid, PPI use, compromised digestive function, SIBO or constipation. High natural resistance to some antibiotics, which may result in overgrowth.
Morganella spp.	Gram-negative group in the *Proteobacteria* phylum. May produce histamine. High levels may indicate increased intestinal inflammatory activity. High levels may cause diarrhea, and may also be associated with SIBO.
Pseudomonas spp. *Pseudomonas aeroginosa*	Gram-negative bacteria in the *Proteobacteria* phylum. High levels may indicate increased intestinal inflammatory activity and may cause abdominal cramping and loose stools. Some strains of *P. aeroginosa* may produce toxins that can damage cells.
Staphylococcus spp. *Staphylococcus aureus*	Gram-positive bacteria in the *Firmicutes* phylum. High levels may result from reduced digestive capacity, and intestinal inflammatory activity. Some strains may produce toxins and contribute to loose stools or diarrhea.
Streptococcus spp.	Gram-positive bacteria in the *Firmicutes* phylum. *Streptococcus* spp. colonize skin and mucous membranes throughout the body; High levels in the intestine may result from low stomach acid, PPI use, reduced digestive capacity, SIBO or constipation; Elevated levels may also be indicative of intestinal inflammatory activity, and may cause loose stools.
Citrobacter spp. *Citrobacter freundii*	Gram-negative bacteria in the *Proteobacteria* phylum. High levels may indicate increased intestinal inflammatory activity.
Klebsiella spp. *Klebsiella pneumoniae*	Gram-negative bacteria in the *Proteobacteria* phylum. Common residents of the oral cavity and respiratory tract. May cause diarrhea, gas, abdominal pain, and bloating; Common after long-term antibiotic use; May release histamine in the gut; High levels may indicate increased intestinal inflammatory activity.
Mycobacterium avium subsp. paratuberculosis	Bacterial species in the *Actinobacteria* phylum. Higher levels have been associated with Crohn's disease and rheumatoid arthritis.
Prevotella copri	Gram-negative species in the *Bacteroidetes* phylum. Associated with rheumatoid arthritis. High levels may result from reduced digestive capacity, or a high-starch diet.
Proteus spp. *Proteus mirabilis*	Gram-negative bacteria in the *Proteobacteria* phylum. High levels may indicate increased intestinal inflammatory activity; May contribute to loose stools or diarrhea; Pets or wild animals can be a source

Gastrointestinal Bacteria as Potential Autoimmune Triggers

Opportunistic gastrointestinal pathogens are gaining attention for their ability to initiate autoimmune thyroiditis and inflammatory arthritis such as rheumatoid arthritis and ankylosing spondylitis. Klebsiella, Citrobacter and Yersinia species are believed to set off systemic autoimmune disease in certain patients that could contribute to inflammatory arthritis in susceptible individuals.

Yersinia enterocolitica infection has been associated with Hashimoto's thyroiditis and Grave's disease[49] and higher antibodies to Yersinia enterocolitica have been found in these patients[50]. Enterovirus is also associated with immunogenic thyroiditis[51].

Analysis of gastrointestinal microbes is recommended in chronic autoimmune disorders that don't respond to the usual therapies. In healthy individuals, opportunistic pathogens should not present a problem. A healthy gastrointestinal barrier, good levels of commensal flora, and strong immune defenses in the gut should eliminate the potential pathogen within a few weeks, causing little to no symptoms.

However, when the intestinal barrier is breached, normally harmless opportunistic microbes can pass through the barrier, creating extraintestinal infection and illness.

Intestinal permeability, or leaky gut, has been documented in a number of autoimmune diseases: ankylosing spondylitis, rheumatoid arthritis, celiac disease, inflammatory bowel disease, IgA nephropathy, nonalcoholic steatohepatitis, and multiple sclerosis[52][53].

Patients with these conditions or documented intestinal permeability may be at risk if gut microbiota are imbalanced.

---

[49] Tomer Y, Davies TF. Infection, thyroid disease, and autoimmunity. Endocr Rev. 1993;14(1):107- 120
[50] Petru G, Stunzner D, Lind P, Eber O, Mose JR. [Antibodies to Yersinia enterocolitica in immunogenic thyroid diseases]. Acta medica Austriaca. 1987;14(1):11-14
[51] Desailloud R, Hober D. Viruses and thyroiditis: an update. Virology journal. 2009;6:5
[52] Fasano A, Shea-Donohue T. Mechanisms of disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases. Nature clinical practice. 2005;2(9):416- 422.
[53] Tiwana H, Wilson C, Walmsley RS, et al. Antibody responses to gut bacteria in ankylosing spondylitis, rheumatoid arthritis, Crohn's disease and ulcerative colitis. Rheumatology international. 1997;17(1):11-16

Molecular Mimicry

Some theories of microbial-initiated autoimmune disease are molecular mimicry, the bystander effect, and the hygiene hypothesis. Molecular mimicry is a common explanation for how a microbial infection can initiate autoimmune disease, presumably due to antibacterial and cross-reactive autoantibodies[54].

It is believed that microbial antigens resemble self-antigens. These cross-reactions essentially "confuse" the immune system which mistakenly mounts an attack against self-tissues. The bystander effect theory proposes that microorganisms damage self-tissues, exposing self-antigens to immune attack. Finally, the hygiene hypothesis presumes that decreased exposure to microbes increases the Th1 response which can lead to autoimmunity[55].

Spondyloarthropathies are a family of chronic, multisystem, inflammatory diseases involving the sacroiliac joints and axial skeleton and they may have an infectious trigger[56]. They include:

- ankylosing spondylitis
- arthritis associated with ulcerative colitis or Crohn's disease
- psoriatic arthritis, and
- reactive arthritis

All of these share a genetic predisposition and all are characterized by inflammation of the sites where ligaments and tendons insert into the bone. They are usually rheumatoid factor negative and they show an association with human leukocyte antigen B27 (HLA-B27).

A prominent hypothesis is that HLA-B27 may resemble or act as a receptor for bacterial antigens, triggering the autoimmune attack on self.

Reactive arthritis can be brought on by genitourinary infections with Proteus mirabilis or gastrointestinal infections with bacterial agents such as Chlamydia, Salmonella, Shigella, Campylobacter, Yersinia and Clostridium difficile.

Parasites such as Strongyloides stercoralis, Giardia lamblia, Ascaris lumbricoides, and Cryptosporidium species can also result in reactive arthritis.

---

[54] Rashid T, Ebringer A. Autoimmunity in Rheumatic Diseases Is Induced by Microbial Infections via Crossreactivity or Molecular Mimicry. Autoimmune diseases. 2012;2012:539282
[55] Fasano A, Shea-Donohue T. Mechanisms of disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases. Nature clinical practice. 2005;2(9):416- 422
[56] Brent LH, Diamond HS. Ankylosing spondylitis and undifferentiated spondyloarthropathy. Drugs & Diseases 2015; http://emedicine.medscape.com/article/332945-overview. Accessed May 14, 2015

Aggressive cases could evolve into ankylosing spondylitis[57]. Substantial data supports a causative role for Proteus mirabilis in rheumatoid arthritis while ankylosing spondylitis and Crohn's disease have been related to Klebsiella microbial infections[58].

Evidence of Salmonella has been found in cases of ankylosing spondylitis. Other data shows abnormal serum antibody responses to Klebsiella and Proteus mirabilis in the spondyloarthropathies, high levels of IgG antibodies to Klebsiella in patients with ankylosing spondylitis, Crohn's disease, and ulcerative colitis, and antibodies to Proteus in rheumatoid arthritis.

While cultures of synovial fluid do not yield gastrointestinal microbes, there is evidence of bacterial antigen and immune responses in the synovium of the joint, suggesting that microbes do play a role in the pathology.

Fecal studies have not been used to provide firm evidence of the causative relationship of stool microbes with autoimmune syndromes. However, stool testing for opportunistic pathogens seems a reasonable avenue in chronic, intractable, and painful autoimmune conditions, especially if onset closely followed a gastrointestinal infection.

Mycobacterium avium subspecies paratuberculosis (MAP) is an obligate pathogenic bacterium in the genus Mycobacterium[59]. It is often abbreviated M. paratuberculosis or M. avium ssp. paratuberculosis. It is the causative agent of Johne's disease, which affects ruminants such as cattle, and suspected causative agent in human Crohn's disease and rheumatoid arthritis[60].

MAP has been found in larger numbers within the intestines of Crohn's disease patients[61] and in significant amount of irritable bowel syndrome patients[62] compared to those suffering from ulcerative colitis or otherwise healthy controls. One study concluded that MAP "may act as a causative agent, have a role in the context of secondary infection, which may exacerbate the disease, or represent non-pathogenic colonisation."[63]

MAP is susceptible to antibiotics used to treat Mycobacterium avium disease, such as rifabutin and clarithromycin, however the capacity of these antibiotics to eradicate MAP infection in vivo has not been established.

[57] Palazzi C, Olivieri I, D'Amico E, Pennese E, Petricca A. Management of reactive arthritis. Expert opinion on pharmacotherapy. 2004;5(1):61-70.

[58] Rashid T, Ebringer A. Autoimmunity in Rheumatic Diseases Is Induced by Microbial Infections via Crossreactivity or Molecular Mimicry. Autoimmune diseases. 2012;2012:539282

[59] https://en.wikipedia.org/wiki/Mycobacterium_avium_subspecies_paratuberculosis

[60] https://medicalxpress.com/news/2018-01-bacteria-linked-rheumatoid-arthritis.html

[61] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1379400

[62] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2168579

[63] Feller, Martin; Huwiler, Karin; Stephan, Roger; Altpeter, Ekkehardt; Shang, Aijing; Furrer, Hansjakob; Pfyffer, Gaby E; Jemmi, Thomas; Baumgartner, Andreas; Egger, Matthias (2007). "Mycobacterium avium subspecies paratuberculosis and Crohn's disease: A systematic review and meta-analysis". The Lancet Infectious Diseases. 7 (9): 607–613.

A study looking into antibacterial activities of naturally occurring compounds found that the most effective compound was trans-cinnamaldehyde, followed by cinnamon oil , and oregano oil. [64]

Klebsiella species

These are gram-negative bacteria normally found in the intestinal tract that are associated with a wide range of small intestinal disorders including alterations of motility, diarrhea, gas, abdominal pain, and bloating. Its overgrowth in the small intestine can also cause histaminosis and gut inflammation through the release of histamine by the bacteria[65]. Those with a history of long-term antibiotic use are at risk.

Prevotella copri

Subgroups of rheumatoid arthritis patients have differential IgG or IgA immune reactivity with P copri, which appears to be specific for this disease. These observations provide evidence that P copri is immune-relevant in RA pathogenesis.[66]

In a study on patients with new-onset RA (NORA) Prevotella copri was over-expanded in stool samples compared with patients with chronic RA (CRA), psoriatic arthritis, or healthy people[67]. In NORA patients, Prevotella abundance in the gut was at the expense of Bacteroides fragilis, an organism that is important for T-regulatory function.

A study in mice showed that dysbiosis contributes to arthritis development via activation of autoreactive T cells in the intestine[68].

The findings of a study indicate that P copri might be a significant etiologic agent in facilitating the progression of RA, or that the inflammation elicited by a variety of microorganisms, including P copri (dysbiosis), might contribute to the perpetuation of RA.[69]

---

[64] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2565950/
[65] Keyzer JJ, van Saene HK, van den Berg GA, Wolthers BG. Influence of decontamination of the digestive tract on the urinary excretion of histamine and some of its metabolites. Agents and actions. 1984;15(3-4):238-241.
[66] https://www.ncbi.nlm.nih.gov/pubmed/27863183
[67] Scher JU, Sczesnak A, Longman RS, Segata N, Ubeda C, Bielski C, et al. Expansion of intestinal Prevotella copri correlates with enhanced susceptibility to arthritis. Elife. 2013;2:e01202.
[68] Maeda Y, Kurakawa T, Umemoto E, Motooka D, Ito Y, Gotoh K, et al. Dysbiosis contributes to arthritis development via activation of autoreactive T cells in the intestine. Arthritis Rheumatol. 2016 doi: 10.1002/art.39783
[69] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5129594/

It can be reduced by a low-carb diet and red wine, amongst others. [70]

Fungal Organisms

Fungal organisms are a part of the normal human digestive tract, but fungal overgrowth can cause illness in susceptible people. Common symptoms associated with fungal overgrowth are gas, bloating, constipation, diarrhea, eczema, and other signs of fungal infection such as athlete's foot, vaginal yeast infections, thrush, and jock itch.

Stool testing, using GI-MAP, for fungi such as Candida, Microsporidia, and Geotrichum can often reveal a hidden source of continual fungal growth– the gut.

Fungal overgrowth is usually controlled with a diet low in sugars and starches. In some cases antifungal medications are necessary.

Microsporidia species were first identified as parasites of the silkworm, but are now recognized as fungi. They are often difficult to diagnose but significant progress has been made with molecular diagnostics for detection of these organisms.

These opportunistic pathogens often infect immunosuppressed individuals such as those with HIV infection, organ transplantation, or chemotherapy, but can also infect healthy people. Common symptoms include diarrhea and wasting due to enteric infection, but the spectrum of related diseases due to these pathogens also includes sinusitis, bronchitis, pneumonia, nephritis, myositis, hepatitis, encephalitis, and other brain infections[71].

Questions still exist about whether microsporidia infections remain persistent in asymptomatic immune-competent individuals, reactivate during conditions of immune compromise, or may be transmitted to others at risk, such as during pregnancy or through organ donation.

Effective commercial therapies for Enterocytozoon bieneusi, the most common microsporidian species identified in humans, are still lacking[72]. Treatment often includes antifungal medications along with diet and nutritional interventions to help with chronic diarrhea.

---

[70] https://cfsremission.com/2017/10/14/decreasing-prevotella-genus/
[71] Ghosh K, Weiss LM. Molecular diagnostic tests for microsporidia. Interdisciplinary perspectives on infectious diseases. 2009;2009:926521
[72] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3109650/

Viruses

Cytomegalovirus

Epidemiology

This is a herpes virus that has infected 60% of the US population. One in three children have contracted CMV by five years old. It is passed around in child daycare centers.

Clinical Implications

Positive CMV on the GI-MAP indicates active infection of the GI, NOT past infection. An active infection may be asymptomatic or cause mild flu-like symptoms.

CMV can also cause viral pneumonia, transaminitis, splenomegaly, colitis, fever, and encephalitis. It is commonly found in inflammatory bowel disease, and immunocompromised patients. CMV colitis has a similar presentation to Clostridium difficile infection.

CMV has been implicated in autoimmune diseases:

- lupus,
- systemic sclerosis, type 1 diabetes,
- and rheumatoid arthritis

Therapeutic Options and Considerations

No treatment is needed if patients are asymptomatic. It is important to prevent spreading CMV with regular handwashing.

Antiviral herbs such as cat's claw, osha root, reishi mushrooms, vitamins A, C, and D, zinc, Echinacea can help.

It is important to address other imbalances on the GI-MAP using the functional 5R Protocol to rebuild gut health and gut immunity.

Epstein Barr Virus

Epidemiology

EBV is one of the most common viruses worldwide; it infects 90–95% of the population, is commonly contracted in childhood and usually only causes mild symptoms.

Clinical Implications

A positive finding on the GI-MAP indicates active EBV infection of the GI, not past infections. It can cause infectious mononucleosis (mono).

Symptoms include fatigue, fever, swollen lymph nodes, inflamed throat, enlarged spleen, and more. They may last two to four weeks in adolescents and adults, but can cause fatigue for weeks or months.

EBV infection is associated with autoimmune conditions such as rheumatoid arthritis, lupus, Sjogren's, multiple sclerosis, and autoimmune thyroid disorders.

EBV may increase the risk of gastric cancer; especially if H. pylori present. It may cause colitis.

The virus is found in 30–64% of IBD patients.

Therapeutic Options and Considerations

Rest and hydration are important. Antiviral herbs such as cat's claw, osha root; antiviral fungi such as

reishi and/or Cordyceps mushrooms and Echinacea can help; Vitamins A, C, and D, and zinc can be supplemented.

Other imbalances on the GI-MAP and the 5R Protocol to rebuild gut health and gut immunity need to be considered.

A follow-up blood testing may be indicated, including an EBV Early Antigen and EBV PCR test.

Opportunistic Parasites

Non-pathogenic parasites are present in the gastrointestinal tract and generally are self-limiting and do not cause illness. However, some research shows an association between non-pathogenic parasites and gastrointestinal symptoms[73].

Therefore, testing of these microorganisms may be useful in some cases. Recent research shows certain parasites, such as Blastocystis hominis, as an emerging potential pathogen[74].

Blastocystis hominis

is found throughout the world in both people with and without symptoms. Common signs of infection with Blastocystis include diarrhea or watery stools, abdominal pain, anal itching, constipation, excess gas, and dermatologic issues. Some research recommends treatment for people with gastrointestinal and dermatologic symptoms but no treatment for those who are asymptomatic[75].

There may also be an association between Blastocystis and chronic digestive disorders, such as irritable bowel syndrome[76].

Chilomastix mesnili

is considered non pathogenic. The presence of cysts and/or trophozoites in stool specimens can however be an indicator of fecal contamination of a food or water source, and thus does not rule-out other parasitic infections.

Cyclospora cayetanensis

Cyclosporiasis is an intestinal illness caused by the microscopic parasite **Cyclospora cayetanensis**. People can become infected with Cyclospora by consuming food or water contaminated with the

---

[73] Dagci H, Kurt O, Demirel M, et al. Epidemiological and diagnostic features of blastocystis infection in symptomatic patients in izmir province, Turkey. Iranian journal of parasitology. 2014;9(4):519-529
[74] Basak S, Rajurkar MN, Mallick SK. Detection of Blastocystis hominis: a controversial human pathogen. Parasitology research. 2014;113(1):261-265
[75] Coyle CM, Varughese J, Weiss LM, Tanowitz HB. Blastocystis: to treat or not to treat. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2012;54(1):105-110.
[76] Tan KS. New insights on classification, identification, and clinical relevance of Blastocystis spp. Clinical microbiology reviews. 2008;21(4):639-665.

parasite. People living or traveling in countries where cyclosporiasis is endemic may be at increased risk for infection.

The time between becoming infected and becoming sick is usually about 1 week. Cyclospora infects the small intestine (bowel) and usually causes watery diarrhea, with frequent, sometimes explosive, bowel movements. Other common symptoms include loss of appetite, weight loss, stomach cramps/pain, bloating, increased gas, nausea, and fatigue. Vomiting, body aches, headache, fever, and other flu-like symptoms may be noted. Some people who are infected with Cyclospora do not have any symptoms.[77]

Treatment[78]

If cyclospora isn't treated, the illness may last from a few days to a month or longer. Symptoms may seem to go away and then return more than once. It's common to feel very tired.

Cyclospora is treated with a course of antibiotics called co-trimoxazole.

Alternatively, treatment with Oil of Oregano is expected to be effective.[79]

Dientamoeba fragilis is a parasite that causes gastrointestinal problems. Despite its name, Dientamoeba fragilis is not an amoeba but a flagellate. This protozoan parasite produces trophozoites; cysts have not been identified. Infection may be either symptomatic or asymptomatic.

There exists a growing body of case reports from numerous countries around the world that have linked this parasite to numerous clinical manifestations. A number of studies have even incriminated D. fragilis as a cause of irritable bowel syndrome[80], allergic colitis[81], and diarrhoea in human immunodeficiency virus patients. As it is often found in people with other co infections there has been some on-going doubt about its validity as a pathogen.

Colonisation may occur without development of disease. In adults, asymptomatic colonisation is present in 75-85% of individuals affected by the parasite. In children, the opposite is true; disease develops in as many as 90% of those colonised.

Symptoms include:

- Anorexia
- Weight loss

---

[77] https://www.cdc.gov/parasites/cyclosporiasis/gen_info/faqs.html#what_cyclo
[78] https://www.nhs.uk/conditions/cyclospora/
[79] https://patentimages.storage.googleapis.com/5a/11/22/9f7fb72d38af28/US5955086.pdf
[80] Yakoob J, Jafri W, Beg MA, Abbas Z, Naz S, Islam M, Khan R. Blastocystis hominis and Dientamoeba fragilis in patients fulfilling irritable bowel syndrome criteria. Parasitol Res. 2010 Aug;107(3):679-84. Epub 2010 Jun 8
[81] Yamamoto-Furusho JK, Torijano-Carrera E. Intestinal protozoa infections among patients with ulcerative colitis: prevalence and impact on clinical disease course. Digestion. 2010;82(1):18-23. Epub 2010 Feb 9

- Nausea
- Vomiting
- Bloating
- Flatulence
- Alternating constipation and diarrhoea
- Headache
- Fever
- Malaise
- Fatigue
- Irritability
- Weakness
- Pruritus
- Urticaria
- Frequency

Conventional Treatment

Presently, Iodoquinol and Tetracycline are the most commonly employed medications, but a recent study found the antiaomebic drug Secnidazole to be highly effective. D. fragilis was eradicated in 34 of 35 patients after receiving a single dose of Secnidazole. A second dose was required only for one patient.[8],[9]

Natural Therapy

The successful eradication of D.fragilis will not occur with either therapy on a consistent basis, that is drugs and natural therapies have a high failure rate.

In children the need for successful management of this organism is just as important but requires care in the selection of medicines and or non drug treatment.

- Saccharomyces Boulardii up to 30 billion CFU's daily
- Bifidus (Colonic Bacteria) species and lower small intestinal species in divided doses with food up to 30 billion CFU's
- Standardised Extract of Garlic 1000mg – 2000mg per day – this is a low risk broad antifungal/parasitic suggestion and may be used away from the probiotics suggested above.
- A combination of Wormwood, Berberine, Citrus Seed Extract & Black Walnut prepared in active forms. These traditional herbs require liver enzyme monitoring if used for more than 30 consecutive days.
- Colloidal Silver – the use of silver solutions are indicated but there is no direct evidence of efficacy in this parasite treatment. However it is easy to administer and if inclined to consider this: Silver 50 once per day
- Artemesia standardised extract

Control measures to limit spread of parasites include the following:

- Disinfect surfaces and equipment handled by children infected by the parasite.
- Disinfect nappy areas.
- Separate nappy areas from food preparation sites.
- Educate about handwashing techniques.
- Improve personal hygiene.
- Separate symptomatic individuals.

Endolimax nana belongs to the least well described non pathogenic intestinal protozoa. Endolimax is transmitted through fecal-oral contamination of food or water. There is very little evidence that Endolimax cold cause diarrhea or intestinal inflammation[82].

Entamoeba coli and **E. hartmanni** are intestinal amebae that are found in the large intestine. They generally are not considered pathogenic. However, when these amebae are found in stool samples it can indicate the presence of other potentially pathogenic organisms.

Pentatrichomonas hominis is considered non pathogenic. The presence of trophozoites in stool specimens can however be an indicator of fecal contamination of a food or water source, and thus does not rule-out other parasitic infections[83].

In women with vaginosis, consider treatment to reduce chances of vaginal contamination or reinfection. If treatment is needed, consider a broad-spectrum antiparasitic herbal formula, including probiotics and the 5R Protocol.

---

[82] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4778187/
[83] https://www.cdc.gov/dpdx/pentatrichomonas/index.html

WORMS

Ancylostoma duodenale and Necator americanus (Hookworms)

Epidemiology

Infection occurs via skin contact with soil contaminated with larvae or ingestion of larvae. Infected cats and dogs are a source of exposure. The worms are prevalent in southern Europe, Northern Africa, India, Asia, Caribbean islands, South America, and small areas of the United States.

Infections are associated with poor sanitation, inadequate housing construction, and lack of access to medications.

Clinical Implications

Early symptoms are itching and rash where the larvae penetrated the skin. Symptoms of heavy infestations include: abdominal pain, diarrhea, fatigue, weight loss, iron deficiency anemia (IDA), coughing, and loss of appetite.

Infected individuals may also be asymptomatic.

Therapeutic Options and Considerations

Heavy infections can be treated with albendazole or mebendazole. Individuals presenting with IDA may need iron supplementation. Anti-parasitic herbal treatments and gut immunity support should be considered.

Ascaris lumbricoides (Roundworm)

Epidemiology

Infection is caused by fecal contamination of food or water and found commonly in international travellers and recent immigrants from Latin America and Asia.

Clinical Implications

Early symptoms include fever, coughing, wheezing, and dyspnea. Late symptoms include abdominal pain, nausea, vomiting, frequent throat clearing, dry cough, "tingling throat," appendicitis, pancreatitis, and obstruction. Infection has been linked to reactive arthritis.

Therapeutic Options and Considerations

Infections may be treated with albendazole, mebendazole, or ivermectin. Anti-parasitic herbal treatments and gut immunity support should be considered.

Necator Americanus

Hookworm[84] is the second most common human helminthic infection (after ascariasis). Hookworm species are worldwide in distribution, mostly in areas with moist, warm climate. N. americanus is found in Africa, Asia and the Americas and predominates in the Americas and Australia. It requires a transpulmonary migration phase for its life cycle.

Iron deficiency anemia (caused by blood loss at the site of intestinal attachment of the adult worms) is the most common symptom of hookworm infection, and can be accompanied by cardiac complications. Gastrointestinal and nutritional/metabolic symptoms can also occur. In addition, local skin manifestations ('ground itch') can occur during penetration by the filariform (L3) larvae, and respiratory symptoms can be observed during pulmonary migration of the larvae.

The most common manifestation of zoonotic infection with animal hookworm species is cutaneous larva migrans, also known as ground itch, where migrating larvae cause an intensely pruritic

---

[84] https://www.cdc.gov/dpdx/hookworm/index.html

serpiginous track in the upper dermis. Less commonly, larvae may migrate to the bowel lumen and cause an eosinophilic enteritis.

Trichuris trichiura (Whipworm)

Epidemiology

It can be transferred via fecal contamination of produce or person-to-person contact. The worm is prevalent in Asia, Africa, South America, and rural southeastern United States

Clinical Implications

Most individuals are asymptomatic, however diarrhea with mucus and blood may occur in some infected individuals

Therapeutic Options and Considerations

Heavy infections can be treated with albendazole or mebendazole. Individuals presenting with IDA may need iron supplementation. Anti-parasitic herbal treatments and gut immunity support should be considered.

Taenia spp. (Tapeworm)

Epidemiology

Infection is caused by fecal contamination of undercooked pork (T. solium) or beef (T. saginata).

T. solium is found worldwide, but prevalent in communities who raise and eat pigs. T. saginata is prevalent in Africa, parts of Eastern Europe, the Philippines, and Latin America where people raise cattle and eat raw beef.

Clinical Implications

Infected people may be asymptomatic or present with mild symptoms, which include: abdominal pain, nausea, weakness, increased appetite, loss of appetite, headache, constipation, dizziness, diarrhea, pruritus ani, hyperexcitability, and anemia

Therapeutic Options and Considerations

Infections may be treated with albendazole or praziquantel. Anti-parasitic herbal treatments and gut immunity support should be considered.

Intestinal Health Markers

The GI-MAP includes markers of immune function, inflammation, digestion, and gliadin sensitivity, and metabolic activity of the gastrointestinal biome. These markers were selected for their clinical utility.

Digestion

Pancreatic elastase 1

This is an excellent global marker of pancreatic exocrine function and can be an indicator of poor digestive capacity or pancreatitis when extremely low. Elastase 1 is unaffected by pancreatic enzyme replacement therapy.

Pancreatic elastase is an enzyme produced by the pancreas to help break down proteins. Pancreatic insufficiency occurs when the pancreas is not working well and becomes inflamed (pancreatitis). This can impair the body's ability to absorb nutrients from food, including fat-soluble vitamins[85].

This test also accurately predicts a patient's response to pancreatic enzyme supplementation, especially in patients with unexplained diarrhea and suspected pancreatic insufficiency[86].

The fecal pancreatic elastase-1 test may also be useful for monitoring diabetics because both insulin and non-insulin-dependent diabetes can impair pancreatic function[87].

---

[85] Turner RC, McDermott R. Using faecal elastase-1 to screen for chronic pancreatitis in patients admitted with acute pancreatitis. HPB : the official journal of the International Hepato Pancreato Biliary Association. 2006;8(3):223-226.
[86] Elphick DA, Kapur K. Comparing the urinary pancreolauryl ratio and faecal elastase-1 as indicators of pancreatic insufficiency in clinical practice. Pancreatology : official journal of the International Association of Pancreatology. 2005;5(2-3):196-200
[87] Cavalot F, Bonomo K, Fiora E, Gaia E, Trovati M. Pancreatic elastase-1 in stools, a marker of exocrine pancreas function, correlates with both residual beta-cell secretion and metabolic control in type 1 diabetic subjects: response to Mueller et al. Diabetes care. 2005;28(11):2810-2811.

Fecal Elastase-1 Result	Clinical Significance
< 200 ug/g	Pancreatic insufficiency
200–500 ug/g	Decreased pancreatic output
> 500 ug/g	Normal pancreatic output

Causes of Low Elastase 1:

- Suppressed pancreatic function
- Gallstones
- Hypochlorhydria, especially if H. pylori present
- Cystic fibrosis
- Low levels may be found in vegetarians/vegans

Common Approaches for Addressing Low Pancreatic Digestive Enzyme Levels:

- Digestive support with betaine HCL
- Chew thoroughly and relax at meal time
- Pepsin
- Plant or pancreatic enzyme supplements
- Digestive herbs
- Bile salts
- Taurine

Steatocrit

Fecal fats are normally emulsified by bile salts and absorbed in the small intestines. The steatocrit is a measure of the amount of fat in faeces, expressed as a percentage.

High levels of fat in the stool may be an indication of maldigestion, or malabsorption, resulting in steatorrhea. This generally results from pancreatic exocrine insufficiency but can also occur with severe small bowel disease i.e. celiac disease, liver diseases such as Primary Biliary Cirrhosis or medications that inhibit fat absorption such as orlistat.

Causes of Elevated Steatocrit include Hypochlorhydria, Maldigestion, Malabsorption, Pancreatic insufficiency (see elastase-1), Bile salt insufficiency, Improper mastication, and Celiac disease.

Therapeutic Approaches and Considerations for High Fecal Fats:

- Support digestion with betaine HCL
- Pepsin
- Digestive herbs or "bitters"
- Bile salts
- Taurine

Underlying causes of malabsorption, such as celiac disease, dysbiosis, or food sensitivities should be considered.

GI Markers

Beta-glucuronidase

Beta-glucuronidase is an enzyme produced by cells in the liver, kidney, intestinal epithelium, endocrine, and reproductive organs. However, this enzyme is also produced excessively by bacteria known to be pathogenic, and high levels may be an indication of adverse metabolic activity of the intestinal microbiome, indicate dysbiosis and interference with Phase II detoxification involving glucuronidation.

Glucuronidation by way of beta-glucuronidase is a major route of detoxification in the human body[88].

However, this enzyme can also convert pro-carcinogens to carcinogenic compounds[89]. High levels of fecal beta-glucuronidase can indicate unfavorable changes in the colon. When the enzyme is elevated in plasma, there is an increased risk of hormone-sensitive cancers, such as those of the breast or prostate.

Evidence of increased enzymatic activity of intestinal microorganisms may suggest increased risk of digestive tract cancer[90].

---

[88] Li Y, Zhang X, Wang L, Zhou Y, Hassan JS, Li M. Distribution and gene mutation of enteric flora carrying beta-glucuronidase among patients with colorectal cancer. Int J Clin Exp Med. 2015;8(4):5310-5316.
[89] Mroczynska M, Galecka M, Szachta P, Kamoda D, Libudzisz Z, Roszak D. Beta-glucuronidase and Beta-glucosidase activity in stool specimens of children with inflammatory bowel disease. Polish journal of microbiology / Polskie Towarzystwo Mikrobiologow = The Polish Society of Microbiologists. 2013;62(3):319-325.
[90] Mroczynska M, Libudzisz Z. Beta-glucuronidase and beta-glucosidase activity of Lactobacillus and Enterococcus isolated from human feces. Polish journal of microbiology / Polskie

Toxins stimulate B-glucuronidase activity and dietary red meat and protein increases the enzyme. Antibiotics increase B-glucuronidase levels. A low-calorie, vegetarian diet can reduce fecal B-glucuronidase levels.

Clinical Indications of High β-glucuronidase:

- Dysbiosis in the colon or small intestinal bacterial overgrowth (SIBO)
- Extremely elevated cases associated with colon cancer risk
- Problems with detoxification, especially estrogen (via glucuronidation pathway)
- Overexposure to toxins or drugs

Therapeutic Approaches and Considerations for Elevated β-glucuronidase:

- Address dysbiosis, if present
- Promote bacterial diversity with probiotics, fiber, prebiotics, and fermented foods
- Consider liver support such as milk thistle and calcium D-glucarate, especially if patient is taking hormone replacement or has increased cancer risk
- If there are no signs of dysbiosis on the GI-MAP, consider a SIBO breath test

Occult Blood Fecal - FIT

FIT is quantitative and directly measures the concentration of hemoglobin present in stool, rather than just the qualitative presence of hemoglobin. This test uses antibodies specific for human hemoglobin and therefore does not require dietary restrictions or multiple samples, significantly reducing the appearance of false positives.

This method has better detection of lower hemoglobin concentrations than qualitative tests, eliminating potential false negatives as well.

Literature suggests a result of 10 ug/g may be indicative of potentially more serious conditions such as polyps or colorectal cancer.

A variety of ailments can cause lower counts of blood in stool, such as hemorrhoids, anal fissures, pathogenic infection such as giardia, liver disease, and upper GI infections.

Possible Causes of Positive Occult Blood:

- Bleeding ulcer
- Inflammatory bowel disease
- Cancer
- Intestinal polyps

- Upper GI bleeds that cause iron deficiency anemia

A gastroscopy and colonoscopy to identify the bleeding source are recommended.

Immune Response

Secretory IgA

This is the body's first line of defense in the gut. A portion of this immunoglobulin might be directed toward gliadin, indicating an immune reaction to the common protein in wheat and other field grass grains.

Secretory Immunoglobulin A (sIgA) is an antibody protein secreted into the gastrointestinal tract as a first line of immune defense against pathogenic microorganisms[91]. This immunoglobulin influences the gut microbiome and helps to maintain barrier function[92] by forming complexes with gut pathogens and allergens, preventing them from penetrating the intestinal barrier.

Impairment of secretory IgA may increase the risk of infectious, allergic, and inflammatory diseases of the intestine[93]. Chronic stress may also disrupt levels of sIgA. Elevated levels of sIgA may indicate an activated immune response to chronic infections or inflammatory reactions.

Therapeutic Approaches for Low SIgA Levels:

- Address any chronic GI infections, if appropriate
- Address microbiome imbalances
- Address chronic stress and adrenal health, if needed
- Colostrum or immunoglobulins
- Supplement with S. Boulardii
- GI mucosal support with glutamine
- Lactobacillus and Bifidobacteria probiotics
- General immune support
- Essential fatty acids

[91] Rogier EW, Frantz AL, Bruno ME, Kaetzel CS. Secretory IgA is Concentrated in the Outer Layer of Colonic Mucus along with Gut Bacteria. Pathogens. 2014;3(2):390-403

[92] Corthesy B. Secretory immunoglobulin A: well beyond immune exclusion at mucosal surfaces. Immunopharmacology and immunotoxicology. 2009;31(2):174-179

[93] Kaetzel CS. Cooperativity among secretory IgA, the polymeric immunoglobulin receptor, and the gut microbiota promotes host-microbial mutualism. Immunology letters. 2014;162(2 Pt A):10-21

- Zinc
- Address other imbalances on the GI-MAP

High Fecal SIgA indicates an elevated immune response to antigens in the GI tract.

Therapeutic Approaches for High SIgA Levels:

- Address GI infections
- Address any food allergies and sensitivities
- General immune support

Anti-gliadin antibodies

The presence of fecal anti-gliadin antibodies can indicate an immune response to gluten in the diet. Gliadin is a component of gluten, the protein found in wheat and other field grass grains such as barley, malt and rye. Because gliadin could stimulate intestinal immunity and increase levels of fecal anti-gliadin antibody even when serum concentrations are undetectable[94][95] it is often used as marker for non-celiac gluten sensitivity. High levels of fecal anti-gliadin antibodies can provide clinicians with an effective treatment strategy: a gluten-free diet.

Inflammation

Calprotectin

Calprotectin helps the integrative and functional medicine practitioner measure the level of immune activation in the gut, often associated with infection and/or inflammatory bowel disease.

Fecal calprotectin is the most studied marker of gastrointestinal inflammation[96] and the gold standard marker for the diagnosis and monitoring of inflammatory bowel disease (IBD)[97].

---

[94] Haas L, Meillet D, Kapel N, Rostoker G, Gobert JG. Increased concentrations of fecal anti-gliadin IgA antibodies in untreated celiac disease. Clinical chemistry. 1993;39(4):696-697.
[95] Halblaub JM, Renno J, Kempf A, Bartel J, Schmidt-Gayk H. Comparison of different salivary and fecal antibodies for the diagnosis of celiac disease. Clinical laboratory. 2004;50(9-10):551-557
[96] Walsham NE, Sherwood RA. Fecal calprotectin in inflammatory bowel disease. Clinical and experimental gastroenterology. 2016;9:21-29.
[97] Siddiqui I, Majid H, Abid S. Update on clinical and research application of fecal biomarkers for gastrointestinal diseases. World J Gastrointest Pharmacol Ther. 2017;8(1):39-46.

Fecal calprotectin levels are proportional to the level of inflammation in the gut. Calprotectin has been shown to correlate with histologic and endoscopic measures of inflammatory bowel disease severity. It is non-invasive, stable, and shows a considerable sensitivity and specificity of 93% and 96%, respectively, when used to screen for IBD activity.

High calprotectin can also be detected in colorectal cancers, diverticular disease, and infectious gastroenteritis.

When IBD is suspected based on clinical presentation, a fecal calprotectin level <50 ug/g stool suggests IBS, not IBD. Calprotectin levels between 50 and 150 ug/g indicate GI inflammation and deserve treatment and follow-up testing. Calprotectin levels greater than 150 ug/g suggest organic disease such as IBD or colorectal cancer and follow-up **colonoscopy** is recommended.

Fecal calprotectin can elevate with enteropathy caused by excessive non-steroidal anti inflammatory medication use. For this reason, it may be beneficial to temporarily discontinue NSAIDs, when possible in select patients, prior to measuring fecal calprotectin[98].

---
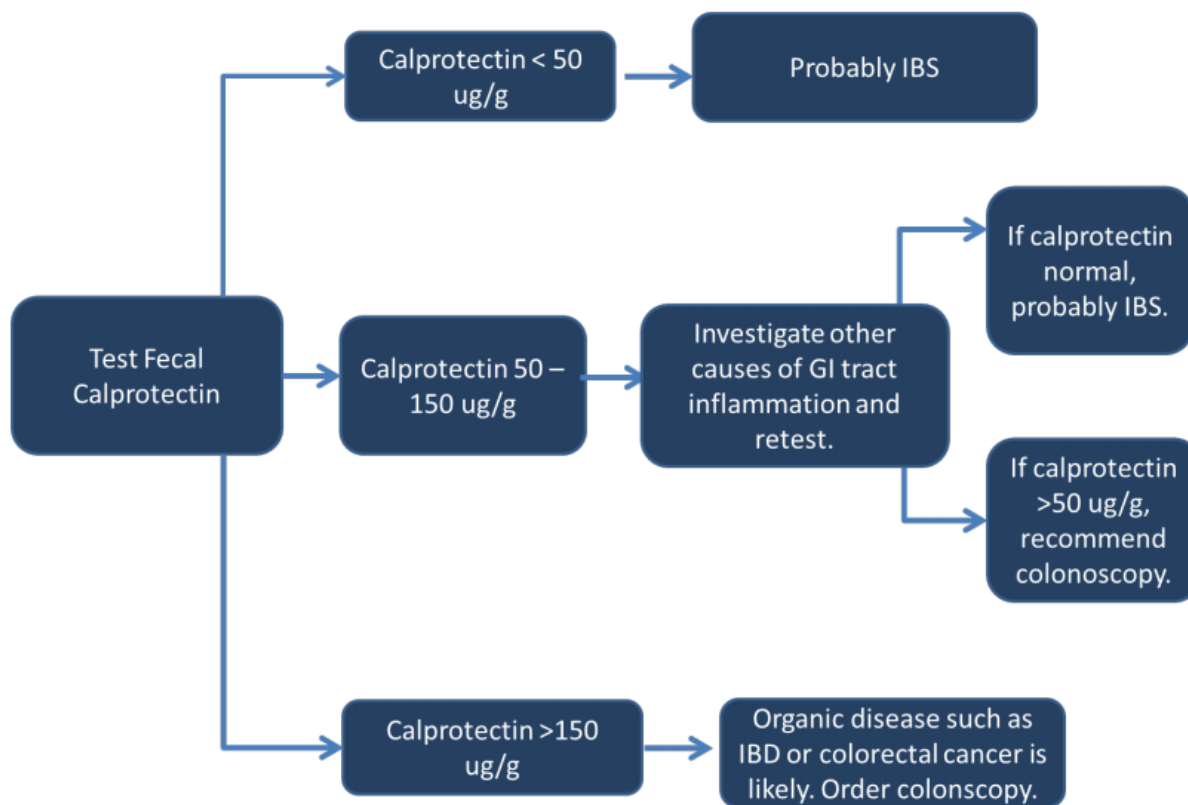
[98] Klingberg E, Strid H, Stahl A, et al. A longitudinal study of fecal calprotectin and the development of inflammatory bowel disease in ankylosing spondylitis. Arthritis research & therapy. 2017;19(1):21.

Zonulin

Zonulin is a protein secreted by intestinal cells that regulates intercellular tight junctions. Tight junctions are the connections between epithelial cells that make up the gastrointestinal lining.

Zonulin increases intestinal permeability in the jejunum and ileum and is considered a biomarker for barrier permeability[99]. Tight junctions can be opened or closed, depending on the physiological need.

Zonulin's role is to open tight junctions in the gut. In the case of enteric infections, high zonulin can "open the floodgates" and flush out bacteria and toxins. Certain gut bacteria and gliadin (the main staple protein from wheat) can activate the zonulin system.

The intestinal barrier is a critical interface between the lumen of the gut and the internal milieu. Dysfunction of this barrier is believed to initiate immune dysfunction because it allows macromolecules from the gut lumen to pass into the bloodstream[100].

Intestinal permeability, also known as "leaky gut," has been associated with inflammatory bowel disease, celiac disease, food allergy, irritable bowel syndrome, critical illness, autoimmune diseases[101], and obesity and metabolic disease[102].

In many cases, permeability precedes disease. Zonulin regulates barrier permeability. Serum zonulin correlates with intestinal permeability and lactulose/mannitol tests for intestinal permeability.

High serum zonulin has been associated with celiac disease, type 1 diabetes, insulin resistance and type 2 diabetes, cancers, neurological conditions, and autoimmune diseases.

---

[99] Lamprecht M, Bogner S, Schippinger G, et al. Probiotic supplementation affects markers of intestinal barrier, oxidation, and inflammation in trained men; a randomized, double-blinded, placebo-controlled trial. Journal of the International Society of Sports Nutrition. 2012;9(1):45
[100] Fasano A. Leaky gut and autoimmune diseases. Clinical reviews in allergy & immunology. 2012;42(1):71-78
[101] Fasano A. Physiological, pathological, and therapeutic implications of zonulin-mediated intestinal barrier modulation: living life on the edge of the wall. The American journal of pathology. 2008;173(5):1243-1252.
[102] Bischoff SC, Barbara G, Buurman W, et al. Intestinal permeability--a new target for disease prevention and therapy. BMC gastroenterology. 2014;14:189.

In athletes, fecal zonulin levels improved (decreased) after 14 weeks of probiotic supplementation[103]. Treatment with zeolite lowered stool levels of zonulin in athletes and presumably improved intestinal barrier function[104].

Drug Resistance Genes

These are genes carried by bacteria that confer a special resistance or protection from certain antibiotics. For most antibiotics there are several different genes. The gene type is dependent on the mode of resistance and the organism(s) it may be found in.

In the GI-MAP, the antibiotic and drug resistance genes for an antibiotic are measured based on the pathogenic organism found to be positive in the fecal sample. Results are reported for the genotypic resistance, meaning the AR gene specific to the positive organism, and globally, meaning all other AR Genes for that drug found throughout the microbiota.

Helicobacter pylori

The standard first line 7-day treatment for H. pylori as per NICE includes:

ANTIBIOTIC*	PROTON PUMP INHIBITOR
Amoxicillin 1g twice daily and either: Clarithromycin 500mg twice daily or Metronidazole 400mg twice daily** **Penicillin allergy** Metronidazole 400mg twice daily and Clarithromycin 250mg twice daily	Esomeprazole 20mg twice daily or Lansoprazole 30mg twice daily or Omeprazole 20–40mg twice daily or Pantoprazole 40mg twice daily or Rabeprazole 20mg twice daily

---

[103] Lamprecht M, Bogner S, Schippinger G, et al. Probiotic supplementation affects markers of intestinal barrier, oxidation, and inflammation in trained men; a randomized, double-blinded, placebo-controlled trial. Journal of the International Society of Sports Nutrition. 2012;9(1):45
[104] Lamprecht M, Bogner S, Steinbauer K, et al. Effects of zeolite supplementation on parameters of intestinal barrier integrity, inflammation, redoxbiology and performance in aerobically trained subjects. Journal of the International Society of Sports Nutrition. 2015;12:40

In order to identify the best treatment plan, GI-Map tests Clarithromycin as a commonly used antibiotic for an existing drug resistance gene.

If any SNP is detected (present), then the H. pylori strain/s are resistant to that class of antibiotics. If for example the patient's H. pylori is resistant to the clarithromycin class of antibiotics it would be prudent to use a different antibiotic when tailoring a treatment protocol.

Fluoroquinolones are antibiotics that are commonly used to treat a variety of illnesses such as respiratory and urinary tract infections. These medicines include ciprofloxacin (Cipro), gemifloxacin (Factive), levofloxacin (Levaquin), moxifloxacin (Avelox), norfloxacin (Noroxin), and ofloxacin (Floxin).

β-lactam antibiotics (beta-lactam antibiotics) are a class of broad-spectrum antibiotics, consisting of all antibiotic agents that contain a beta-lactam ring in their molecular structures. This includes penicillin derivatives (penams), cephalosporins (cephems), monobactams, and carbapenems.[1] Most β-lactam antibiotics work by inhibiting cell wall biosynthesis in the bacterial organism and are the most widely used group of antibiotics. Until 2003, when measured by sales, more than half of all commercially available antibiotics in use were β-lactam compounds.[2]

Bacteria often develop resistance to β-lactam antibiotics by synthesizing a β-lactamase, an enzyme that attacks the β-lactam ring. To overcome this resistance, β-lactam antibiotics are often given with β-lactamase inhibitors such as clavulanic acid [Co-Amoxicillin].

Macrolide antibiotics are: azithromycin (brand name Zithromax), clarithromycin (brand names Klacid and Klacid LA), erythromycin (brand names Erymax, Erythrocin, Erythroped and Erythroped A), spiramycin (no brand), and telithromycin (brand name Ketek).

About CountryHealth

Private GP Practice with Focus on Functional Medicine

Our patients usually get in touch when they need help that the NHS cannot provide. We can advise you on symptoms, organise specialist tests that are often not available on the NHS and can also refer you privately to specialists. We want to find the root cause of your problems, not just cover the symptoms with medication.

As a private medical patient, you can expect more personal, friendly consultations and appointments at times that suit YOU.

To fully explore your concerns, we don't limit you to "one problem per 10 minute appointment". Instead our appointments take typically 30-60 minutes. Unfortunately, we cannot offer A&E services.

Our approach is different. We want to find the root cause of your problems, not just cover the symptoms with medication.

We offer a range of services to our clients to help them to Get Well and Stay Well.

- Health Screenings
- Genetic Testing
- Nutritional / Functional Therapy
- Food Intolerance Testing

To find out more, please visit our website: www.CountryHealth.co.uk

Practice:

CountryHealth
Cornwallis Chambers
23 Great Colman Street
Ipswich
IP4 2AN

Phone : 01473 218 373
Email: reception@countryhealth.co.uk