Obesity and Intestinal Bacteria
Mark Pimentel, MD

In the last decade, there has been an exponentially growing interest in the human microbiome as it relates to health and disease. There are many bacterial ecosystems in the human body, such as the sinus and vaginal tracts. None of these, however, are as large and diverse as the digestive tract, which is home to more than 500 species of bacteria and believed to contain 10 times more bacterial cells than there are human cells in the body. This tremendous biodiversity must surely contribute in many ways to the host. Recent research has tried to examine the beneficial and detrimental effects of these bacteria.

One means of correlating the gut microbiome to human health and disease is to characterize the entire composition of bacteria in both type and proportions—in essence, a bacterial bioprint. Driving this activity is the premise that humans have a specific range of bacteria and bacterial composition that is to be expected in a healthy individual. Alterations in composition of these bacteria might lead to the development of conditions such as colon cancer, inflammatory bowel disease and even systemic illnesses.

The challenge with studying the human microbiome, and gastrointestinal bacteria in particular, lies in the many factors involved. Diverse cultural, ethnic and socioeconomic backgrounds can have significant influence, since ethnicity may determine the types of food ingested and consequently impact intestinal flora. Socioeconomic background might also reduce the quantity of food ingested, resulting in a lower quantity of gut bacteria. Furthermore, each individual—through environmental exposure to various bacteria—learns to immunologically “tolerate” a specific colonization profile. This tolerance leads to variations between individuals who are otherwise normal. Finally, a variety of other external forces are involved. For example, proton pump inhibitors might increase the penetration of oral bacteria into the gut, and antibiotic use could have a dramatic influence on gut flora.

Despite these complexities, the field has rapidly advanced in many areas. An area of great interest is the role of gut bacteria in the obesity epidemic. While obesity is a multifaceted problem, recent data suggest that gut bacteria may play a role. In animal studies, transplantation of gut flora from obese animals led to an increased weight among the transplanted mice (1). This and other data support a hypothesis that the type and quantity of bacteria in the gut may be important. People with obesity may have a bacterial composition that more readily liberates calories from food items.

As part of this work in obesity and gut microbes, methane-producing organisms appear to be standing out in a growing number of studies attributing gut flora to obesity. In a germ-free animal model, co-colonization of Methanobrevibacter smithii and Bacteroides was associated with an increase in body weight that was not seen with Bacteroides alone (2). An extensive analysis of the metabolic products in this model suggested that a synergy in calorie harvest was seen. A recent human study in three obese subjects supports this data (3).

In work conducted at Cedars-Sinai, gut bacteria and specifically bacterial overgrowth has been demonstrated as important in irritable bowel syndrome (IBS) (4). An extension of this work demonstrated that methane production on breath test was associated with the constipation form of IBS (5). This was later proven to be related to methane effects on transit (6). This research suggests another potential role of methane in the development of obesity. By slowing transit, it is possible that methane production by humans allows more time to liberate calories from a meal.

To examine the possible role of methane in human obesity, researchers at Cedars-Sinai examined obese (BMI 30-60 kg/m2) individuals and obtained breath samples to evaluate for methane production. The data presented at this year’s Digestive Diseases Week demonstrated that obese subjects

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Esophageal Dysfunction in Patients with Severe Pulmonary Disease

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Lung transplantation is an evolving therapy for severe pulmonary diseases. Unfortunately, rejection of the transplanted lung continues to be a relatively common and vexing problem that does not respond adequately to immunosuppressive therapies. Gastroesophageal reflux is associated with a number of pulmonary diseases and is now a recognized cause of lung transplant rejection. It is not known, however, if disorders of pharyngo-esophageal motor function play a pathogenic role in the genesis of severe pulmonary diseases or transplant rejection.

Gastroenterologists, pulmonologists and thoracic surgeons at Cedars-Sinai set out to explore this question by evaluating the pharyngo-esophageal motor function of lung transplant candidates. Patients were evaluated with a technique called high-resolution esophageal manometry (HRM). The technique displays esophageal motor function as pressure topographic plot in which pressure is displayed as colors (Figure 1). Transplant candidates also had 24-hour ambulatory intravesophageal pH studies to evaluate them for gastroesophageal reflux.

Esophageal motor abnormalities that may predispose patients to either abnormal esophageal acid exposure or aspiration were frequently found in lung transplant candidates. Fully two-thirds of patients had a hypotensive lower esophageal sphincter and 40 percent had a hiatus hernia. Three-quarters had peristaltic dysfunction in the smooth muscle esophagus—either failed or hypotensive peristalsis (Figure 2). There was also a surprisingly high incidence of pharyngeal abnormalities that may lead to aspiration. These included a hypotensive upper esophageal sphincter in 20 percent (Figure 3) and an elevated pharyngeal bolus pressure in 13 percent (Figure 4). An elevated pharyngeal bolus pressure is indicative of a cricopharyngeal bar or pharyngeal motor dysfunction. Thirty-six percent of patients had excessive acid exposure in the distal esophagus and 25 percent in the proximal esophagus. These data suggest that diagnostic tools like HRM and pH testing have a role in the evaluation of patients with severe pulmonary problems.

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Figure 1: A normal HRM color pressure topographic plot. Pressure is represented by color in the HRM color contour (color bar). Sensor location is on the Y-axis and time is on the X-axis. Upper esophageal sphincter (UES) and lower esophageal sphincter (LES) pressures are seen as horizontal bands of color indicating higher pressures than in the adjacent pharynx, esophagus or stomach. Opening of the UES and LES relaxation are depicted as changes to color that indicate a lower pressure: UES pressure approximates that in the esophagus (*), and LES pressure approximates that in the stomach (**). The peristaltic pressure wave is portrayed as a diagonal band of color running from the UES to the LES. It has a higher pressure in the striated muscle segment, diminishes over the transition zone and increases in amplitude in the smooth muscle esophagus. Pressure in the swallowed bolus is a slight, simultaneous rise in intravesophageal pressure (arrow) that occurs shortly after initiation of the water swallow. It remains elevated ahead of the peristaltic pressure wave. The black arrowhead indicates diaphragmatic contraction during LES relaxation. Figure 2: Failed peristalsis and hypotensive LES. A wet swallow (WS) did not produce normal peristalsis in the smooth muscle esophagus. At the GE junction, contraction of the diaphragm is seen as pressure increases in association with inspiration. During expiration, pressure at the GE junction drops to approximate intragastric pressure, indicating that LES resting pressure is low. There are very short duration openings of the UES that are not associated with swallowing (*). This patient had a small burp that coincided with this opening event.
Inflammatory bowel disease patients have an increased risk of gastrointestinal (GI) cytomegalovirus (CMV) infection due to several factors, including the use of immunosuppressive drugs, GI inflammation, malnutrition and possible immune dysregulation. However, the exact relationship between CMV and IBD remains unclear—whether CMV infection predisposes susceptible individuals to develop IBD, or unmasks and exacerbates existing IBD, or simply reflects colonization of rapidly dividing, dysplastic or inflamed tissue and is not pathologic. While prior studies showed increased colectomy and mortality rates in IBD patients with CMV and improved remission rates with antiviral treatment, the role of routine antiviral therapy for all IBD patients with CMV infection and the severity of CMV infection on clinical outcomes had not been examined.

These unanswered questions inspired a retrospective chart review of IBD patients with CMV infection on pathology specimens. Patients were stratified into three histologic groups: 1) no evidence of CMV, 2) “light infection” defined by the absence of viral inclusion bodies on routine haematoxylin and eosin (H&E) stains but positive CMV immunohistochemistry (IHC) stains against CMV monoclonal antigens, and 3) “heavy infection” defined by presence of viral inclusion bodies on both routine H&E and special IHC stains.

Overall, evidence of any CMV infection was noted in 43 out of more than 600 patients with active symptoms, 20 of whom were stratified into the light CMV group and 23 into the heavy CMV group. There was no difference between light and heavy CMV groups in regards to gender, age, tobacco use, underlying diagnosis, duration of disease, steroid or immunomodulator use, or disease-specific activity scores. Colectomy rates were higher in all patients with evidence of CMV infection compared to our baseline population (30%) whereas the heavy CMV infection group had a 57% colectomy rate (p<0.05, Figure 1A).

When comparing those treated with intravenous (IV) antiviral therapy vs. those untreated, colectomy rates in all CMV patients was 38% vs. 57% (p=0.19, Figure 1B). When stratified by light and heavy CMV, the light CMV group demonstrated a nearly identical colectomy rate among those treated and untreated (31% vs. 29%, p=0.72). The heavy CMV group, on the other hand, demonstrated a trend towards a decreased colectomy rate when comparing treated vs. untreated patients (44% vs. 83%, p=0.07).

Peripheral CMV polymerase chain reaction (PCR) levels were lower in patients with light CMV compared to heavy CMV (45 vs. 179, p<0.05, Figure 1C). Interestingly, peripheral CMV PCR levels were lower in all CMV patients requiring colectomy compared to those who avoided surgery (50 vs. 190, p<0.05).

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To our knowledge, this is the first study to examine the severity of CMV infection on clinical outcome and response to antiviral therapy. We show that heavy CMV infection is associated with higher colectomy rates than light CMV infection. Our data also indicate that patients with heavy CMV infection on either histology or peripheral CMV PCR, CMV may be the main driver of gut inflammation, and anti-viral therapy is effective in treating the inflammatory process and avoiding colectomy. In contrast, IBD patients with light CMV infection on either histology or peripheral CMV PCR, the underlying IBD may be the main driver for gut inflammation. Therefore, treating IBD using immunosuppressants may improve clinical outcome. Further studies are needed to independently verify these results. Our study may help to manage clinical expectations in IBD patients presenting with active GI symptoms and CMV infection, and serve as an initial step towards developing a guideline for the treatment of IBD patient with varying degrees of CMV infection.

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with methane on their breath had a 6-point greater BMI than those without methane, and this was true in multivariate analysis as well. Further work presented at this year’s meeting demonstrated that methane production in humans was associated with the presence of Methanobrevibacter smithii in stool.

Understanding the relationship between gut bacteria and human disease will continue to evolve. However, there appears to be growing evidence for the role of Methanobrevibacter smithii in the production of constipation (in the case of IBS) and now perhaps in some cases of obesity.

 References:

Figure 1: Severity of CMV infection with colectomy and anti-viral therapy response in IBD patients. Heavy CMV infection is associated with a higher colectomy rate (A). Antiviral treatment reduces colectomy rate in IBD patients with heavy CMV infection (B). Boxplot graph showing peripheral CMV PCR is correlated with heavy CMV and decreased colectomy in IBD patients (C).

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