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Small Intestinal Bacterial Overgrowth in Post Oesophagectomy and Gastrectomy Patients

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By

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DECLARATION

I hereby declare that I am the sole author of this thesis and the material submitted to the Dublin Institute of Technology towards the Masters of Philosphophy is entirely my own work and has not been submitted for any academic assessment other than that of the award mentioned above.

Signed: _____

Date: _____

DEDICATION

I would like to dedicate this thesis to my husband James, my parents Helen and Pat, and to my sister Lorna.

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I wish to acknowledge the contribution made to this work by the following people:

Firstly I would like to thank Ms Patricia Lawlor, my hospital supervisor for all her advice, encouragement and continuing support.

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Last but not least, my husband, James and my family for all your understanding, belief and constant support from the very start of my career, I thank you.

ABSTRACT

A review of patients who underwent a hydrogen breath test for Small Intestinal Bacterial Overgrowth, following an oesophagectomy or gastrectomy was carried out in the Gastrointestinal Function Unit, St. James's Hospital, Dublin.

The aim of this research was to look at the incidence of Small Intestinal Bacterial Overgrowth and create an optimal protocol for Hydrogen Breath Testing with the hope of improving patient compliance and reducing clinic waiting times. Factors such as lifestyle, multimodal therapy, tumour morphology, and gender were analysed in relation to positive Hydrogen Breath Test results in this patient group. Patients were selected following a referral from the upper GI Surgical team. Exclusion criteria included those patients whom had complicated upper major GI surgery, those patients that had their surgery for a non-malignant carcinoma, and those patients that had their surgery for achalasia or a gastric fistula.

Following a strict 12 hour fast and following pre-procedure instructions, the patient's hydrogen breath test was conducted. A preliminary mouth rinse with a chlorhexadine agent was performed followed by a baseline breath sample. A solution of glucose or fructose was consumed and samples were taken every 15 minutes over a two hour period. The patient performed this manoeuvre by holding their breath for approximately 10 seconds and exhaling into the Gastro+ Gastrolyzer® breath monitor. Values were measured in parts per million.

Poor lifestyle factors did not have an effect on the outcome of Hydrogen Breath Test results. Those patients who had a history of previous malignancy and post-operative complications showed a higher tendency towards a positive glucose Hydrogen Breath Test result as did those patients who had a longer post-operative hospital stay. This however, was not statistically significant. The percentage of patients who were positive for Small Intestinal Bacterial Overgrowth (53% in total) was greatest 6-12 months post-surgery. This may be attributed by the fact that intestinal motility including Migrating

Motor Complexes can take up to 12 months before it is restored to its normal functioning state. The positive patient group tested using glucose substrate demonstrated a 93% positivity for SIBO at 60 minutes. Therefore, this suggests that altering the protocol of testing from 2 hours to 60 minutes should be considered

Some patients (up to 10%) are non-hydrogen producers, those who are very symptomatic with negative Hydrogen Breath Tests should be considered for bile acid malabsorption investigation using SeHCAT (tauroselcholic [75 selenium] acid). SeHCAT is now available in St. James's hospital to investigate patients who are symptomatic with steatorrhoea/diarrhoea post-surgery. Small Intestinal Bacterial Overgrowth can be the cause of bile acid malabsorption, therefore it should be considered to treat it with antibiotic therapy and assess clinical response before commencement with prescribed bile acid sequestrants.

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Chapter 1

1 Introduction

Hydrogen Breath Testing (HBT) is a technique that is directly and instantaneously capable of detecting both small intestinal bacterial overgrowth (SIBO) and dietary malabsorption. It is a simple and non-invasive procedure with few cost implications. The patient attends the Gastrointestinal Function unit after adhering to strict pre-procedure guidelines and the specific substrate (glucose, lactulose, or fructose) dissolved in 250mls of water is consumed. The patient is asked at regular intervals of 15 minutes to exhale into the Gastro+ Gastrolyzer® (Gastro+ Operating Manual 2014) HBT machine and a direct read out of Hydrogen in exhaled breath is measured in units of parts per million (ppm). Depending on the values obtained and the substrate consumed, this procedure can take from 90-180 minutes to perform.

Small intestinal bacterial overgrowth, malabsorption of Lactose, Sucrose and Fructose, and Intestinal transit time using Lactulose can all be measured using the HBT. Glucose and Lactulose are the most commonly documented substrates used for detecting SIBO (Simren and Stotzer 2006).

Small intestinal bacterial overgrowth (SIBO) is as the name suggests a bacterial overgrowth within the small intestine. Normally, anaerobic colonic bacteria reside in the large intestine and perform multiple functions to regulate the digestive system. Sometimes, conditions within the gastrointestinal (GI) tract prohibit the defence mechanism to prevent and keep bacterium from colonising within the small intestine. This may include elevated pH within the stomach, dysrhythmic activity altering the intestinal motility, or following GI surgery (DiBaise 2008).

When SIBO is present, the bacteria compete with the normal digestive process and affect the method in which nutrients pass across the lumen of the small intestine. The bacteria essentially ‘eat’ the nutrients (particularly carbohydrates and sugars) entering the intestine and produce by-products as a result. These include gases such as carbon dioxide and hydrogen, and short-chain fatty acids (Eisenmann *et al* 2008). It is these by-products that can cause unpleasant abdominal and GI symptoms such as bloating, flatulence, epigastric and abdominal pain, nausea, early satiety, and altered bowel habit. Patients who complain of such symptoms are often referred to have SIBO investigations performed.

The rate of positive results in the GI function unit when testing for SIBO, is overall quite low. During a data analysis of procedures performed over a two year period, one group of patients with a high positive result for SIBO was evident. This was a surgical group of patients who was referred to the GI function unit post oesophagectomy or gastrectomy that were now complaining of post-surgical symptoms such as those described above in conjunction with malabsorption issues.

The HBT does not impose any discomfort or agitate the patient in any invasive or unwarranted way. Side effects are uncommon and would include those symptoms listed above i.e. the patients’ normal symptomatic response to SIBO. In rare circumstances, patients’ may experience dizziness, allergy-like reactions or tachycardia arrhythmias (Ledochowski M and Ledochowski E 2008). The drawback of this investigation for the patient is the time it takes to perform this study, compliance with the pre-procedure instructions and travelling for their appointment.

In response to the above results, a retrospective study was undertaken on post-surgical patients that were referred to the unit, to investigate the incidence of SIBO. The aim was to determine at what point might SIBO have developed in these patients; and whether factors such as neoadjuvant chemotherapy or radiotherapy, the location of cancer/tumour, previous history of carcinoma, or surgery on the GI tract influenced the development of SIBO.

A comprehensive data analysis of e.g. patient history, lifestyle, co-morbidity factors, complications post-surgery and hydrogen breath test results, was scrutinised to determine if there was a significant aspect or consequence that could result in a greater incidence of developing SIBO.

Factors related to the optimal timing of HBT sampling in post-surgical patients were examined to determine at which point patients were most likely to show a positive result. The overall aim of the present study is to create an optimal protocol for HBT in patients following GI surgery. This is to include the time segments between sampling, so that crucial values of exhaled Hydrogen are not missed due to altered GI physiology.

Chapter 2

2 Anatomy and Physiology

2.1 Gastrointestinal Tract

The GI system consists of the mouth, oral cavity, oesophagus, stomach, small intestine, large intestine, rectum and anus, refer to Figure 2-1. (Martini 2006). The liver and pancreas are associated digestive organs which produce and secrete digestive juices into the small intestine.

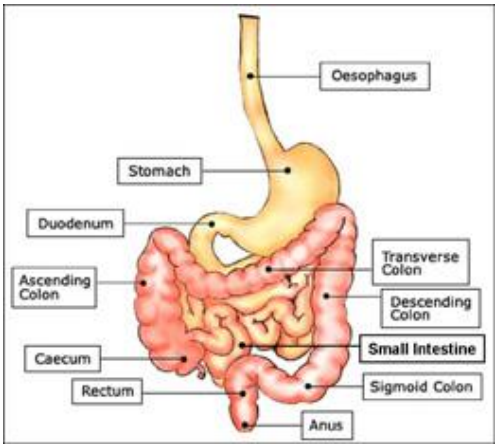

Figure 2-1 - Anatomy of the GI Tract (Visionary Health 2014)

The oesophagus consists of striated muscle in the proximal segment and smooth muscle in the distal two thirds. It is approximately 25 cm in length with two sphincters; the upper oesophageal sphincter (UOS) in the proximal oesophagus and the lower oesophageal sphincter (LOS) in the distal oesophagus. The function of sphincters is to control the direction of flow through the GI tract (Stendal 1997).

The stomach has five main functions; to act as a reservoir for ingested food, to mix and grind food, to chemically break down food, to kill ingested microbes, and to control the emptying of gastric contents into the duodenum. The stomach has a number of important functions as described in Table 2-1 overleaf.

The motility of the stomach and small intestine differs depending on whether a person is fasting or has eaten recently. Migrating motor complexes (MMC) are the dominant pattern in the fasting state. Following ingestion of a meal, MMC are replaced by peristaltic and segmenting and mixing waves (DLGIP 2009). The pacemaker located on the greater curvature (refer to Figure 2-2) of the corpus of the stomach generates electric impulses for gastric motility. These are intense contractions that encourage mixing and grinding of solid food. There is a lag phase of about 30-60 minutes after eating before food is emptied into the duodenum.

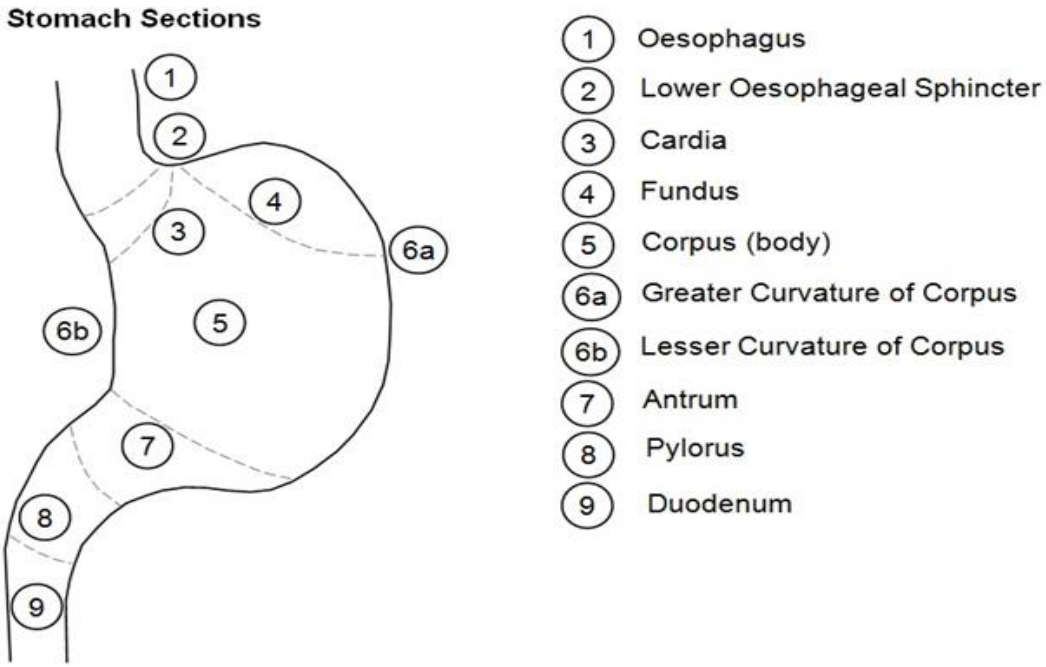

Figure 2-2 - Regions of the Stomach

Table 2-1 - Function of the main regions of the stomach

Region	Function
Cardia	Joins stomach and oesophagus
Fundus	Main Reservoir where ingested food is received
Corpus	H_{CL} and pepsin produced here as well as fundus. Pacemaker area of stomach is located on the greater curvature of corpus
Antrum	Hormone gastin is produced here. There is no H_{CL} secretion in this part. Principal site where solid food particles are ground down before emptied into duodenum
Pylorus	Controls emptying of food into duodenum and limits regurgitation of duodenal contents back into stomach.

The small intestine is approximately 3-5m in length and consists of the duodenum, jejumum and ileum. The main function of the small intestine is the digestion and absorption of nutrients. This is implemented through (1) the mixing of food with digestive juices secreted into the intestinal lumen (2) ensuring the products of digestion come into contact with the absorptive surface of the small intestine and (3) to propel any waste products towards the colon (Stendal 1997). The duodenum is the most proximal portion of the small intestine. It is also the shortest part and extends from the pylorus, around the head of the pancreas and down to the jejunum. The common bile and pancreatic duct which open into the duodenum, allow bile and pancreatic juices to enter this portion of the intestine. The sphincter of Oddi controls the release of these digestive juices into the duodenum (Stendal 1997).

The colon has many functions, the most important of which are; the absorption and secretion of certain electrolytes and water, and the storage and excretion of waste (Gibson and Roberfroid 1995). The large intestine is approximately 1.3m in length and consists of the cecum with its appendix, ascending, transverse, descending and sigmoid colon (Stendal 1997). The ileocecal valve is at the junction of the ileum and cecum and prevents retrograde movement of colonic contents back into the small intestine. It also regulates entry of small intestinal content into the colon.

The colon at birth is a sterile, dark, warm, moist and anaerobic tract. It rapidly fills with food and the above conditions make it an ideal environment for bacteria to grow, therefore rapid colonisation occurs. A gram of caecal content may comprise of 400-500 species of bacteria and up to 2 billion organisms from 17 different bacterial families creating a microbial ecosystem (Chapman 2001). There is a balance between the colonic bacteria and colonic epithelium. If this balance is altered, diarrhoea may result because the colonic epithelium is unable to effectively absorb sufficient quantities of water. This can occur for example as a result of antibiotic therapy and separately, if there is an immune response to the colonising bacteria, mucosal inflammations can occur. This results in diseases such as ulcerative colitis. Finally, if the bacteria cross invasively through the colonic epithelium, sepsis can develop (Chapman 2001).

The gallbladder acts as a reservoir for bile and holds around 20mls of bile juice. Bile is transported from the liver to the gallbladder via the hepatic and cystic duct. The main function of bile is to emulsify fats. It is released in response to hormones secreted by the duodenum, usually in the presence of meals (Stendal 1997). Bile is transported to the duodenum via the cystic and common bile duct. The pancreatic duct is connected at the distal region to the common bile duct where the united channel in most cases empties into the duodenum. The sphincter of Oddi is located here, the function of which is to regulate the entry of pancreatic and bile juice into the duodenum (Stendal 1997).

The pancreas houses two major cell types; exocrine and endocrine. The function of the endocrine cells is the production of insulin, glucagon, and somatostatin which mainly regulate blood sugar levels. The exocrine cells produce and secrete digestive enzymes and bicarbonate ions. With regards to pancreatic secretion, hormonal mediators are more important than neural mechanisms for stimulation of pancreatic juices.

Carbohydrates and fats are the body's main source of energy. Most dietary carbohydrates are in the form of large polysaccharides or disaccharides. In order for these sugars to be absorbed, they must be metabolised by enzymes into their monosaccharide absorbable forms (Simren and Stotzer 2006). Glucose and fatty acids are the main substances metabolised for use by the Krebs cycle to produce energy. The Krebs cycle occurs within the mitochondria of a cell (Martini 2006).

Monosaccharide's have a ring-shaped structure. They are single-sugar units. Disaccharides are formed from two monosaccharide molecules that are bonded together; examples include Lactose, Sucrose and Maltose (Martini 2006). Both monosaccharide's and disaccharides contain only one or two sugar units and so are referred to as simple carbohydrates (Nix 2012). Polysaccharides are long chains of monosaccharide molecules. Examples include starch and glycogen (Martini 2006). They are referred as complex carbohydrates (Nix 2012).

Because monsaccharides are single molecules, they do not need be metabolised and so are readily absorbed across the small intestine. Disaccharides on the other hand need enzymes to break the bond between the molecules. Examples include the lactase enzyme which metabolises lactose into glucose and galactose. Another example is the sucrase enzyme which metabolises sucrose into its monosaccharide components glucose and fructose.

As polysaccharides are more complex structures, metabolism occurs at a much slower rate. Because of this mechanism, energy is released over a longer period of time (Nix 2012).

The physiological effects of carbohydrates apart from energy supply to the biological system includes; the control of blood glucose and insulin metabolism, satiety and gastric emptying, cholesterol and triglyceride metabolism, bowel function, bile acid dehydroxylation and they also affect colonic micoflora (FAO 1997).

Salivary amylase begins the process of carbohydrate digestion. Mastication of food mixes the bolus with saliva and the enzyme amylase initiates the hydrolysis of starch (digestible carbohydrate). Salivary amylase is deactivated by the low pH of the gastric secretions within the stomach but will continue to work if it is in the centre of a food bolus. Gastric secretions will continue to diffuse polysaccharides and other food components. Some carbohydrates have been shown to decrease the rate of gastric emptying. These are carbohydrates that increase the viscosity of gastric contents and this in turn is associated with certain non-starch polysaccharides affecting the glycaemic and insulin responses as well as lowering plasma cholesterol levels. Non-starch polysaccharides are polysaccharides associated with dietary fibre (cellulose, hemicellulose, pectin and gums) and oligosaccharides such as insulin (Schneeman 2007).

Complex carbohydrates are digested by microbial enzymes and therefore have important physiological effects throughout the GI tract as they are not metabolised until they reach the colon. These include their water-holding capacity, increased viscosity within the small intestine, bile acid binding, bulk properties and they are also used for microbial growth in the colon. Increased viscosity within the small intestine has been shown to delay the absorption of sugar. Certain polysaccharides have also shown that they can bind or adsorb bile acids. These effects are associated with the ability of certain polysaccharides to have an effect on glucose and insulin responses as well as the lowering of plasma cholesterol concentrations (Schneeman 2007).

As the chyme enters the small intestine, the presence of protein, fat and acid stimulates pancreatic and bile secretions. Pancreatic amylase continues the hydrolysis of starch. This process of metabolism enables the monosaccharide end products to be absorbed by the intestinal villi. However, not all starch is digested, some remains in the small intestine as ‘resistant starch’. The non-digestible carbohydrates remain intact and continue to the colon.

Residual intestinal material including the resistant starch and non-starch polysaccharides enter the colon through the ileo-cecal valve. The fermentation of these carbohydrates by colonic bacteria produces by-products such as short-chain fatty acids and gases such as hydrogen, carbon and methane. Acetate, propionate, and butyrate are the main short chain fatty acids produced. Colonocytes use butyrate as an energy source, acetate is used by peripheral tissue and muscle cells while propionate is emptied from the portal blood by the liver. The non-digestible carbohydrates have another important role and that is in the elimination of faecal material. They do so both directly by increasing stool mass and indirectly by increasing microbial mass through supporting its growth. The major components of faecal material are water, microbial mass and unabsorbed/undigested food (Schneeman 2007).

Carbohydrates historically were only considered to be required as an energy source, however, carbohydrate binding proteins (lectins) are found on all cell-surface membranes (Osborn 2003). As well as bonding to proteins, carbohydrates also bond to lipids and play an important role in signalling processes on a cellular level (Boysen 2013).

Chapter 3

3 Oesophageal and Gastric Cancer

3.1 Squamous cell carcinoma and Adenocarcinoma

The incidence of oesophageal and gastric cancer is increasing. This is particularly evident with adenocarcinoma of the oesophagus (Griffin and Raimes 2007). In the West, there has been a marked increase in adenocarcinoma of the lower oesophagus and oesophagastric junction over the last 20-30 years (Reynolds *et al* 2010). In particular, Ireland has one of the highest rates of oesophageal cancer in Europe, with approximately 400 new diagnosis each year (Reynolds 2010b).

Oesophageal cancer is three to four times more prevalent in men than women (Fessler and Havrila 2012). Squamous cell carcinoma is usually located in the upper or middle third of the oesophageal body (Surgical Tutor 2014). These tumours are usually in the advanced stage upon detection and approximately three quarters of these tumours will have extended into the muscularis and lymph nodes (Griffin and Raimes 2007). For example, of 100 patients with oesophageal cancer, approximately 50 of these patients will have localised disease that can be treated with curative intent. A small minority of this group may not be treated aggressively because of medical co-morbidities. The five year survival rate is between 35-50 per cent in those patients treated with curative intent (Reynolds 2010b). The overall oesophageal cancer survival rate at five years is 22%. This includes all treatment (including curative) intents and all stages of oesophageal cancer (Ten year cancer audit report 2012).

Adenocarcinoma of the oesophagus can arise from Barrett's oesophagus. This can occur when the normal squamous epithelial cells are exposed to

frequent or long durations of gastric acid exposure. The resulting metaplasia causes the normal squamous cells of the distal oesophageal body to replicate columnar cells, similar to those that line the stomach (Griffin and Raimes 2007). Adenocarcinoma of the oesophagus is usually located in the lower third of the oesophagus.

The risk of developing adenocarcinoma of the oesophagus as a result of Barrett's oesophagus is suggested to be 30 times greater when compared to the general population. For example, approximately 10% of patients with gastro-oesophageal reflux disease will develop Barrett's oesophagus. Of these Barrett's patients, about 1% will progress to develop carcinoma. (Surgical Tutor 2014). Of the patients treated in St. James's Hospital for oesophageal cancer, 66% of these cancers were adenocarcinoma morphology (Ten year cancer audit report 2012).

If high grade Barrett's oesophagus or very early oesophageal cancer is detected, then endoscopic mucosal resection and possibly radiofrequency ablation therapy may be performed instead of surgery (Cancer Research UK 2014). Careful patient selection using endoscopic management appears to reduce morbidity and mortality rates when compared to performing an oesophagectomy. However, the long-term effectiveness of endoscopic therapy needs further evaluation (O'Farrell *et al* 2013).

Obesity is thought to play a role in the development of cancer (Donohoe *et al* 2014). Rates of obesity are increasing rapidly. This is reflected with 65% of men and 56% of women being overweight or obese in the United Kingdom. Adipose tissue is primarily deposited either subcutaneously or centrally (visceral fat). Visceral fat is thought to be more metabolically active and secrets adipokines and cytokines which contributes to systemic inflammation in addition to the expanded adipose tissue infiltrated with macrophages and activated T-cells. According to the World Cancer Research Fund, it is estimated that up to 35% of oesophageal cancers are attributable to obesity (World Cancer Research Fund 2007). Data on the correlation between gastric adenocarcinoma and obesity is limited (Donohoe *et al* 2014).

Symptoms associated with oesophageal cancer include; dysphagia, weight loss, hiccups, odynophagia, and a long history of reflux disease (Walsh *et al* 2011). Unfortunately dysphagia is rarely a symptom of early disease. Aims to reduce mortality from oesophageal cancer include targeting factors such as smoking, obesity, diet and reflux disease, early diagnosis and better cure rates (Reynolds 2010b). Advances in the surgical and multimodal management of patients who present with oesophageal cancer may improve cure rates and survivorship (Croghan *et al* 2015).

Adenocarcinoma of the stomach occurs in the gastric mucosa and accounts for approximately 90% of all malignant gastric tumours. Early gastric cancer is defined as a malignant tumour that is limited to the mucosa or submucosa. They are predominantly found within the lower two-thirds of the stomach. The detection of early gastric cancer can lead to a very good prognosis. (Griffin and Raimes 2007).

The most commonly found factors attributing to the development of gastric cancer include mucosa inflammation, intestinal metaplasia of the gastric mucosa, polyps, chronic peptic ulcer, gastric epithelial dysplasia and more recently Helicobacter pylori has been linked with development of gastric cancer (Griffin and Raimes 2007).

Following a distal gastrectomy for peptic ulcer disease, there is a higher risk of developing cancer. The majority of tumours are found at or near the stoma site. The gastric remnant may be associated with histological changes such as gastritis, polyps and atrophy. There is a two–fold risk of developing cancer when compared to a control group (Griffin and Raimes 2007).

About three quarters of gastrointestinal stromal tumours (GIST) are benign. They are thought be composed of spindle cells with extracellular collagen. They are more common in women and there are often multiple tumours present (Griffin and Raimes 2007).

The overall survival rate at five years for gastric cancer is 23%.This includes all treatment (including curative) intents and all stages of gastric cancer. The five year survival rate in those patients treated with curative intent is 46% according to data published by St. James's Hospital, Dublin (Ten year cancer audit report 2012).

Pre-operative staging is generally carried out to evaluate the extent of the malignancy and to determine if there is any metastatic disease. The cancer cells can spread through tissue, the blood, and the lymphatic system. The investigations that may be carried out help determine the stage of the disease include; endoscopic ultrasound, computerised axial tomography (CAT) scan, positron emission tomography (PET) scan.

St. James's Hospital (National Centre for Oesophageal and Gastric Cancer and the National Centre for Management of Early Upper Gastrointestinal Mucosal Neoplasia), Dublin published a ten year cancer audit report in 2012 outlining trends and referral patterns, measuring and monitoring of quality and care, complexity of treatment, as well as high quality data collection and statistical analysis. In relation to oesophageal and stomach cancer, there has been approximately 100% increase in new referrals over this 10 year period e.g. in 2003 there was 118 patients treated for oesophagogastric cancer increasing to 263 patients in 2012. Of this group, 41% of oesophageal and 35% of gastric cancer patients had a family history of cancer. In 2012, 82 complex major upper gastrointestinal resections were performed, 50 for oesophagectomy and 32 for total gastrectomy (Ten year cancer audit report 2012).

3.2 Radiotherapy and Chemotherapy

The management of oesophageal and gastric cancer may involve treatment with chemotherapy and radiotherapy. They may be given alone, combined, pre-surgery, post-surgery, or both.

Oesophageal cancer is a systemic disease in a vast majority of patients, it requires systemic treatment. Patients treated with pre-operative chemotherapy alone, may have their disease down-staged but surgery is required for curative intent. If however, patients have pre-operative chemo-radiotherapy, up to two thirds (depending on stage) will have a complete pathological response. According to data from Connolly Hospital, Dublin, one-third of patients undergoing chemo-radiotherapy have a complete pathological response to their treatment (Walsh *et al* 2011).

Radiotherapy administered pre-operatively (Neo-adjuvant) is given with the view of reducing the tumour size and reducing the risk of iatrogenic dissemination of tumour cells. Post-operative radiotherapy is performed to eradicate disease at the resection or any suspected residual cancer cells. The disadvantage of post-operative radiotherapy is that the newly reconstructed GI segment may be subject to the full radiation dose which may compromise its function.

Pre-operative chemotherapy is reported to induce early tumour regression and reduce the incidence of drug-resistant tumour cells. The use of chemotherapy post-surgery is often suggested in patients who are at a high risk of recurrence. It is also believed that adjuvant therapy should begin immediately after surgery because of the increased risk of metastases that occurs following the resection of the primary tumour (Griffin and Raimes 2007)

An example of the regime of Radiotherapy and Chemotherapy given in St. James's Hospital is shown in Table 3-1.

Table 3-1 - An Example of a Chemotherapy and Radiotherapy regime

	Duration	Dose/Drug
Radiotherapy	25 sessions over 5 weeks. Mon-Fri over the 5 week duration	41.4 Gy/23 Fractions
Chemotherapy	2 cycles starting on days 1 and 22	Cisplatin80mg/m^2 diluted in 1000ml NaCl 0.9%. Infused over 2-6 hrs. given day 1
		Mannitol 10% 500ml. Infused concurrently with cisplatin over 2-6 hrs. given day 1
		5-Fluorouracil 1000mg/m2 diluted in 1000ml NaCl 0.9%. infused over 24 hours. given days 1-4

3.3 Oesophagectomy and Gastrectomy

Not all oesophageal and gastric cancer patients will be suitable or benefit from GI surgery. Preoperative assessment and staging of cancer is very important in planning treatment options. Neoadjuvant therapy (chemotherapy and/or radiotherapy) usually in combination with surgical resection of the tumour is the most successful outcome for treating oesophageal and gastric malignancies. For those patients that require palliative care, treatments such as stenting may be used to try and alleviate symptoms of oesophageal and gastric cancer (Griffin and Raimes 2007). The patient's anatomy, age, fitness, previous medical history and type/extent/location of the tumour all play important roles in the surgeons approach to each individual case.

Resection of an oesophageal tumour is a very complicated and delicate surgical procedure. It often involves the removal and reconstruction of part or most of the oesophageal body and/or the oesophageal-gastric junction as well as the removal of lymph nodes. This surgical procedure is called an oesophagectomy. If the tumour has extended into the stomach, a partial gastrectomy may also need to be performed (Cancer Research UK 2014).

Different types of oesophagectomies can be performed depending on the location, type and extent of the malignancy. An oesophagectomy may involve a total or partial resection of the oesophagus. The procedure is typically named after the surgeon that developed them:

• Subtotal two stage Oesophagectomy (Ivor-Lewis). Right thoracotomy and abdominal incision with intra-thoracic anastomosis (RCS 2014)

• Subtotal three-stage oesophagectomy (McKeown). Right thoracotomy and abdominal incision with neck incision for anastomosis (RCS 2014)

• Transhiatal Oesophagectomy. Abdominal incision with neck incision for anastomosis

• Minimally invasive oesophagectomy (Thoracosopic +/- lapasroscopic oesophagectomy)

The thoracic incision is made to mobilise the oesophagus while the abdominal incision is performed to prepare the stomach. Reconstruction involves creating a new oesophageal tube by performing an anastomosis to join the stomach to the healthy oesophageal remnant. The anastomosis can be performed via a cervical incision. In those patients with tumours in the lower third of the oesophageal body, a partial oesophagectomy may be performed. This can be carried out transhiatally using only an abdominal incision (NICE 2011).

Surgeons differ in their technique when performing an oesophagectomy and can approach the tumour via the neck, chest or abdomen. Reconstruction of the oesophagus using the stomach as a substitute is the preferred option as it involves only one anastomosis, refer to Figure 3-1 to Figure 3-3 (Griffin and Raimes 2007). However, a part of the small intestine or a colonic transposition can be performed depending on the circumstances, Figure 3-4.

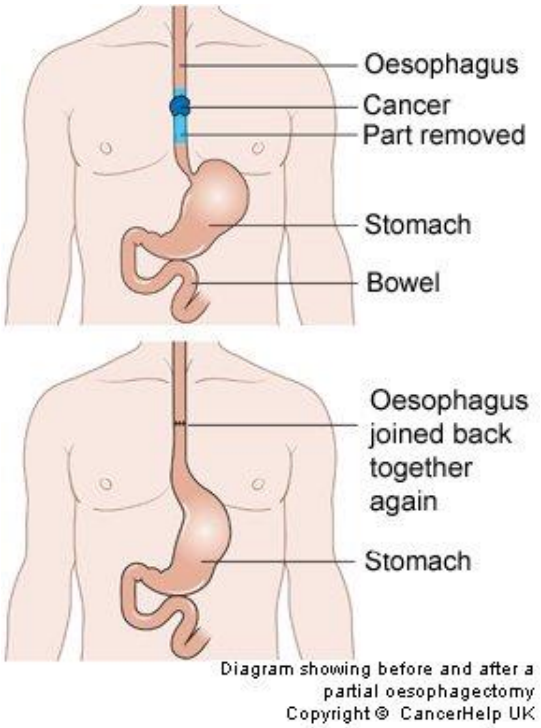

Figure 3-1 - Oesophagectomy with stomach anastomosis

(Cancer Research UK 2014)

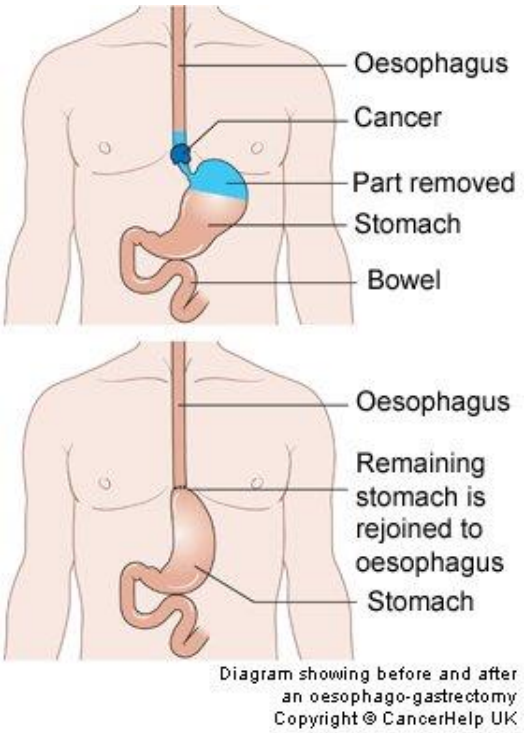

Figure 3-2 - Oesophagectomy with a partial gastrectomy

(Cancer Research UK 2014)

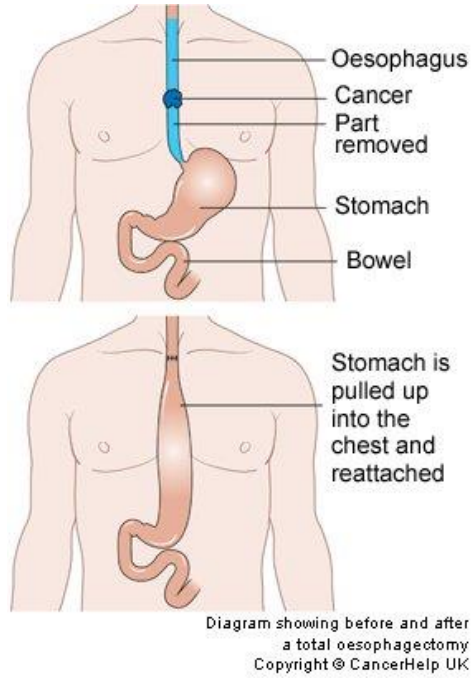

Figure 3-3 - Total oesophagectomy

(Cancer Research UK 2014)

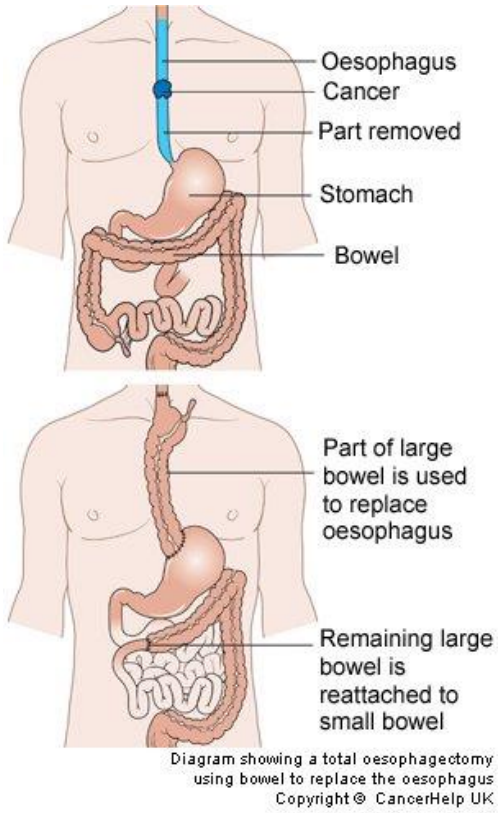

Figure 3-4 - Oesophagectomy with colonic transposition

(Cancer Research UK 2014)

A gastrectomy is a surgical operation involving the removal of the stomach. It may involve the removal of the entire stomach (total gastrectomy) or part of the stomach (partial gastrectomy).

A partial gastrectomy can involve the removal of the proximal stomach or it can be a distal gastric resection. A distal gastrectomy may involve the removal of the antrum, distal two-thirds of the stomach or distal four-fifths of the stomach. A total gastrectomy involves the complete removal of the stomach, gastroesophageal junction and pylorus. Other types of gastrectomy include a wedge resection, sleeve resection, and pylorus-preserving segmental gastrectomy. Laparoscopic partial gastric resections can also be performed. This approach takes more operating time but is thought to be associated with a faster GI recovery time (Wirtzfeld 2014). A lymphadenectomy is usually performed in conjunction with the gastric resection. As mentioned above, each case is tailored by the surgeon depending on the position of the cancer and the margins necessary to ensure complete removal of malignant cells.

One of the most important aims when performing a curative gastrectomy is to ensure complete resection of the malignancy. It has been suggested that resection margins around the tumour should be >2-3cm for early gastric cancer and >2-6cm for advanced gastric cancer (Wirtzfeld 2014).

The most common reconstructions following a partial gastric resection include the Billroth I, Billroth II, and Roux-en-Y. Billroth I (refer to Figure 3-5) preserves duodenal and jejunal connection by anastomosing the remnant stomach to the duodenal stump. The most common complication of this technique is the reflux of biliary contents into the stomach causing alkaline gastritis (Wirtzfeld 2014).

Billroth II preserves the jejunal but not the duodenal connectivity by anastomosing the remnant stomach to the proximal jejunum. It is performed when Billroth I is not feasible. In addition to alkaline gastritis, patients may also experience malabsorption because the duodenal segment is compromised (Wirtzfeld 2014). As can be seen in Figure 3-6, the pancreatic and bile juices do not meet the stomach contents entering the small intestine until they flow down into the jejunum.

Roux-en-Y (refer to Figure 3-7) involves the diversion of biliary drainage away from the gastric remnant. Patients may experience less reflux than if the techniques above were used, but dumping syndrome and gastric atony may be an issue in some (Wirtzfeld 2014). It is usually performed for a total gastrectomy.

Alkaline reflux can be a complication following a gastrectomy, especially if the pyloric and/or lower oesophageal sphincter is resected. The incidence of developing reflux oesophagitis depends on the type of reconstructive surgery. The Roux-en-Y technique is associated with a lower rate of reflux oesophagitis. Factors that affect the incidence of developing alkaline reflux oesophagitis include; the length of the jejunal loop and the site where pancreatic and bile secretions enter the intestines. It is suggested that the jejunal loop should be 35-40cm but ideally over 50cm in length (Matei *et al* 2010).

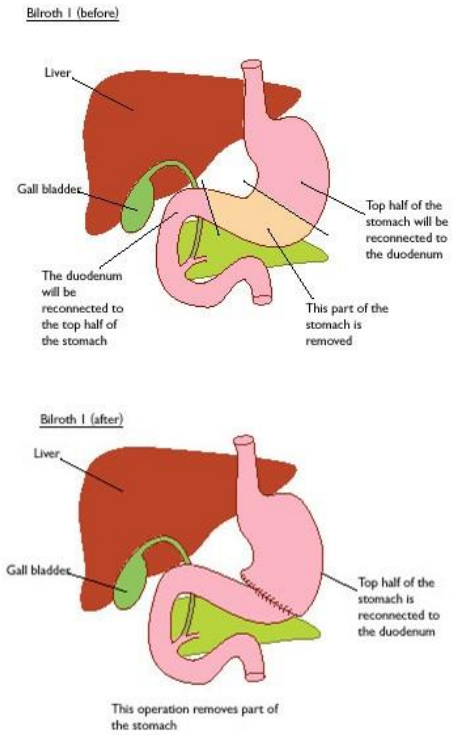

Figure 3-5 - Billroth I reconstruction for gastric carcinoma

(GSI 2014)

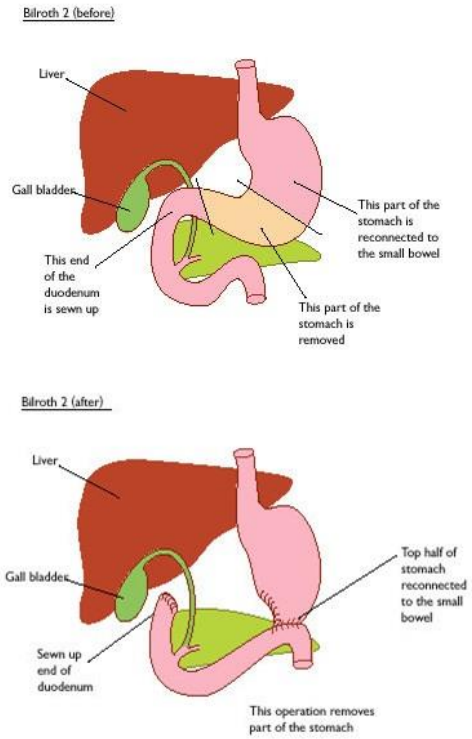

Figure 3-6 - Billroth II reconstruction for gastric carcinoma

(GSI 2014)

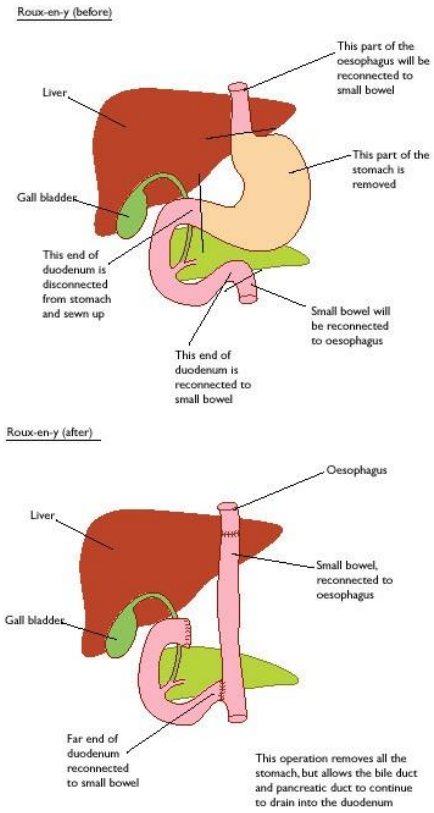

Figure 3-7 - Roux-en-Y reconstruction for gastric carcinoma

(GSI 2014)

Any gastric resection may result in major nutritional consequences for the patient and impact their recovery and quality of life post-surgery (see section 3.4). Therefore the aims of reconstruction for a gastrectomy is to perform the least complex anastomosis to allow adequate nutritional intake. In addition to this, alteration in GI physiology should be kept to a minimum, reflux of intestinal secretions into the oesophagus should be prevented, and the reconstruction should not be prone to long-term complications such as SIBO (Griffin and Raimes 2007).

As with any surgical procedure, complications can occur. These may include general complications or those specific to the oesophageal or gastric resection and reconstruction. Such complications include: haemorrhage, anastomotic leak, intra-abdominal sepsis. Long term complications include: early satiety, dumping syndrome, SIBO, bile reflux and general malnutrition and weight loss (Griffin and Raimes 2007).

3.4 Nutritional consequences of upper GI surgery

Surgical resection of the oesophagus or stomach for cancer may produce varied forms of malabsorption since the GI tract is our major source of nutrients (Lawrence 1977). Malnutrition following an oesophagectomy is common. This surgical procedure results in an altered stomach anatomy – the stomach is now smaller and in a different position. As a result of this, dumping syndrome due to rapid emptying of food into the duodenum can occur. In contrast, some patients may experience delayed gastric emptying because the vagus nerve is cut during surgery (Fessler and Havrila 2012).

Impaired nutrition is more commonly observed after a partial or total gastrectomy when compared to oesophagectomy patients (Lawrence 1977). The stomach plays many important roles in digestion, for example it acts as a reservoir, mixes and grinds food, destroys ingested bacteria, secretes digestive juices and controls the emptying of gastric contents into the duodenum (DLGIP 2009). Therefore, it is not surprising that surgical manipulation and resection of all or part of the stomach has a major effect on nutritional status.

The stomach is a complex organ and has many important functions. This includes its ability to accommodate by dilating in response to a meal without any significant rise in intragastric pressure. Another important function is the controlled release of food from the stomach into the small intestine. This allows the chyme to be mixed with pancreatic, bile and intestinal secretions at a rate which allows optimal digestion and absorption. An intact and nerve stimulated pyloric sphincter is vital to maintain this gastric emptying function. Therefore any gastric resection may result in significant malnutrition for the patient (Griffin and Raimes 2007).

Following a gastrectomy, the impairment of fat absorption plays an important role in malabsorption. Impaired absorption of vitamins (e.g. vitamin B12) and

iron may also occur. The stores of Vitamin B12 are slowly depleted after a total gastrectomy but the development of megaloblastic anaemia has a delayed onset (6 months to 4 years for onset to appear) because the liver has a large store of this vitamin which delays the clinical appearance of B12 deficiency.

Dumping syndrome is a common complaint and one reason is thought to be due to the loss of pyloric function. Symptoms of dumping syndrome include epigastric fullness, hyperperistalsis, nausea, vomiting or diarrhoea. Other non-abdominal symptoms can also occur as early as 15 minutes after ingestion of food such as tachycardia, sweating, weakness and measurable alterations in cardia output and regional blood flow (Ukleja 2006). Dumping syndrome can be divided into two types; early and late. Early dumping syndrome occurs soon after the ingestion of a meal. It occurs because of the rapid emptying of the stomach contents into the intestine. Late dumping occurs about one or more hours after ingestion of a meal. It is caused by excess insulin secretion in response to the stomach's rapid emptying into the small intestine, refer to Figure 3-8. (RCS 2014).

It has been suggested by experimental investigations, that these symptoms occur as a result of a large volume shift into the bowel following a hyperosmolar meal. The large shift of fluid into the intestine is associated with a loss of water from the plasma, and can appear as alteration in cardiac output and redistribution in blood flow, which in turn affects the renal blood flow, the digital blood flow and intestinal blood flow (Lawrence 1977). The rapid entry of food into the intestine can stimulate the pancreas to release insulin causing hypoglycaemia. The inappropriate release of vasoactive GI hormones causes peripheral and splanchnic vasodilatation and vasomotor symptoms such as tachycardia and dizziness (Ukleja 2006).

Low carbohydrate diets (especially simple carbohydrates) are necessary to reduce symptoms while increasing the intake of fibre to slow motility and reduce insulin peaks. Late dumping syndrome which is a consequence of reactive hypoglycaemia occurs 1-3 hours after a meal and approximately 25%

of patients with dumping syndrome will experience this late phase of symptoms. These symptoms include difficulty with concentration, hunger, decreased consciousness, perspiration and tremor (Ukleja 2006).

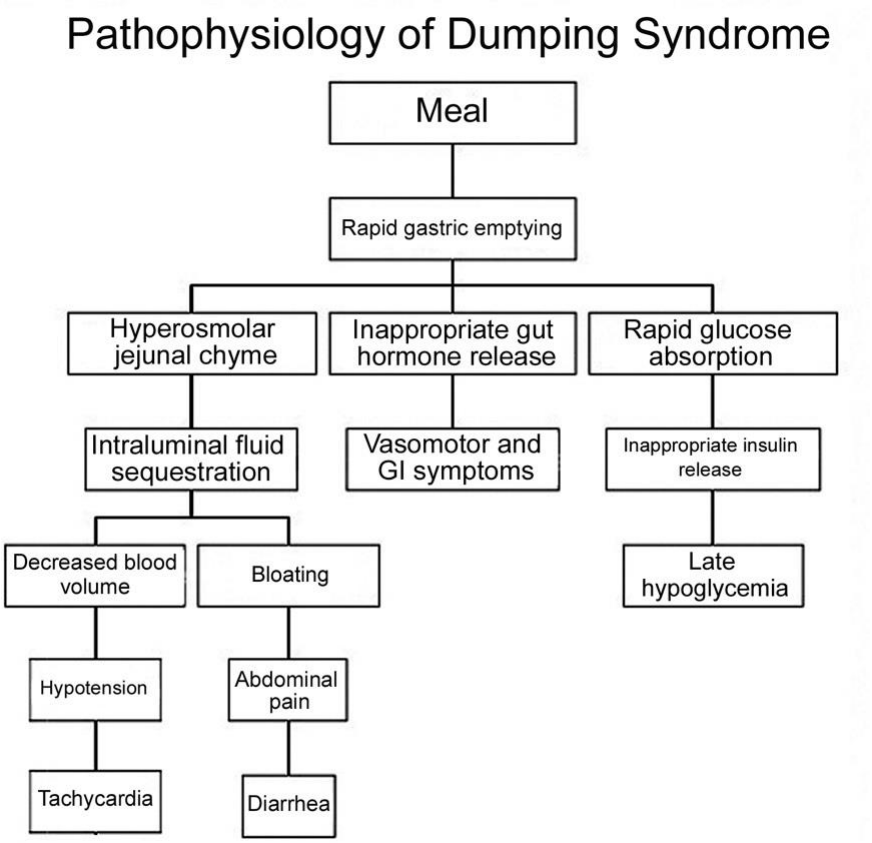

Figure 3-8 - Pathophysiology of Dumping Syndrome

(Kanth 2014)

Chapter 4

4 Bacterial overgrowth of the small intestine

4.1 Pathophysiology of Small Intestinal Bacterial Overgrowth

Small intestinal bacterial overgrowth is usually defined as the presence of $>10^5$ colony forming units (CFU)/mL of bacteria in the proximal small intestine. It has been suggested however, that a lower colony count (e.g. $>10^3$ cfu/mL) may be enough to cause symptoms in an individual (DiBaise 2008). In SIBO, the bacterial species in the small intestine closely resembles the 300-400 species normally present in the colonic region (Zaidel and Lin 2003).

In healthy individuals, it is normal for small numbers of bacteria to be present in the stomach and small intestine. These bacteria are usually gram positive aerobes, anaerobes are rare. Colonic anaerobes (primarily fastidious anaerobes e.g. Bacteroides, anaerobic lactobacilli, and clostridia) are not normally found in the proximal small intestine, which contrasts with the mostly aerobic bacteria in this portion of the intestine (Zaidel and Lin 2003). Lactobacilli are less gas producing than some other bacteria such as Clostrida (Kumar *et al* 2010).

In the distal part of the small intestine, the bacteria more commonly resemble that of the colon. These are mostly gram negative aerobes but with a minor contribution from anaerobes present (Table 4-1). This region is separated by the ileo-cecal valve, which acts like a barrier. At the ileocecal valve, the intestinal transit of luminal contents is slowed, allowing some colonic bacteria to move into the terminal ileum (Shelly 2009). Distal to this valve, the bacteria increase in number and consist mainly of anaerobes, refer to Figure 4-1 (Simren and Stotzer 2006). Bacteria that reside in the proximal colon grow at a fast rate because they have a plentiful supply of dietary nutrients. This

results in a decrease in pH because of the vast short chain fatty acid production. In the distal colon, bacteria are more slow growing as substrate availability is lower and the pH is more neutral (Gibson and Roberfroid 1995).

Table 4-1 - Concentration of bacteria CFU/mL (Simren and Stotzer 2006)

	Stomach	**Jejunum**	**Ileum**	**Caecum**
Aerobes	10^2-10^3	10^2-10^4	10^5-10^8	10^2-10^9
Anaerobes	0	0	10^3-10^7	10^9-10^{12}
Total Count	10^2-10^3	10^2-10^4	10^5-10^8	10^{10}-10^{12}

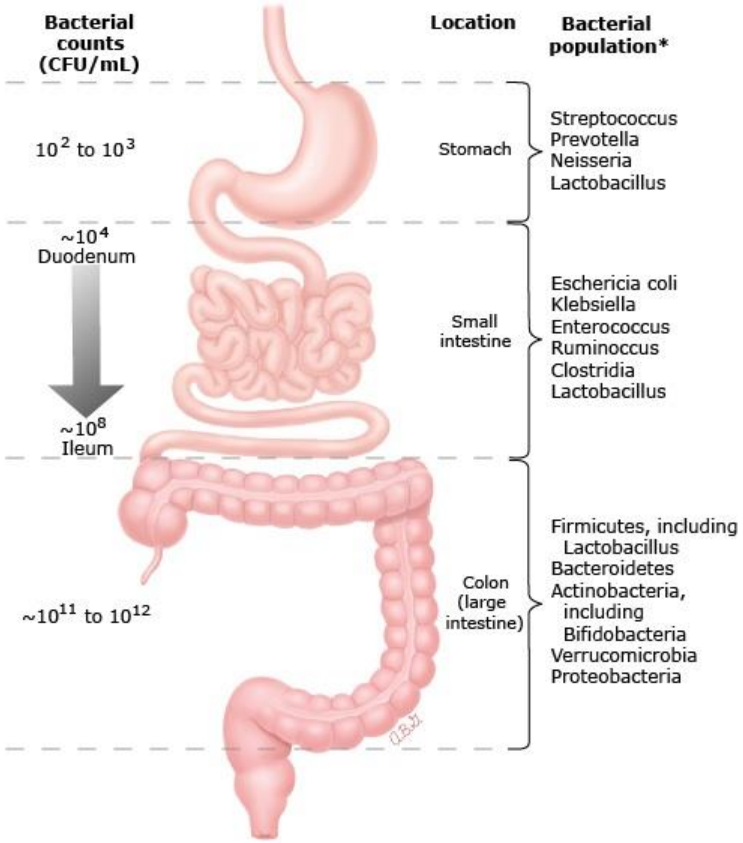

Figure 4-1 - Normal intestinal bacterial flora

(Vanderhoof & Pauley-Hunter 2013b)

* Bacteria are not listed in quantitative order

It must be considered that the total growth rate may consist of an overgrowth of gram positive bacteria. This is mainly due to upper respiratory flora and this is a common finding in the small intestine of healthy elderly people. It is thought that this type of gram positive bacteria is not associated with symptoms of SIBO. In contrast, the gram negative, anaerobes and enterocci bacteria correlate with such symptoms. They also deconjugate bile acids (as discussed in more detail in Section 4.3 'Consequences of SIBO'), affect the binding capacity of intrinsic factor, and reduce the absorptive function of enterocytes (Simren and Stotzer 2006).

It is thought that each individual person has their own distinctive composition of colonic bacteria which appears to be affected by dietary patterns, intake of various nutrients and geographical region. However, it is also suggested that even in those patients with the same diet, the effects of ingested food on individual microflora composition may be very different (Mai and Morris 2014).

The 'Gold Standard' diagnosis of SIBO is believed to be through the culturing of jejunal aspirate. This can be defined as being positive for SIBO if the total growth is $>10^4$ bacteria and/or there is growth of gram negatives or anaerobes (Simren and Stotzer 2006). This however, is not an ideal method of diagnosis since the intestinal bacterial flora may be present in the more distal segment of the small intestine (DiBaise 2008). Technically, direct culture is limited to detecting SIBO in the upper 60cm of the small intestine (Nucera *et al* 2005).This is further emphasised by the high rate of false negative results and the low reproducibility rates (Zaidel and Lin 2003). In addition to this, it is a costly and invasive method, many bacterial species do not grow in routine culture media, contamination of the endoscope and catheter can occur as it passes through the GI tract, and proper handling of the sample is required (Dukowicz *et al* 2007). Culturing of small intestinal aspirates can however, increase the detection rate of SIBO by 12% (Rusu *et al* 2012). Another study by Teo M. *et al* concludes from their findings that duodenal fluid aspiration and culture is the most accurate method of testing for SIBO with high specificity when compared to hydrogen breath testing. This study however, used a different methodology for their HBT findings (Teo *et al* 2004).

There are numerous factors and 'defence' mechanisms involved to prevent SIBO, and control the bacterial population in the small intestine. The two major features include; gastric acid secretion which inactivates and destroys many organisms before they enter the proximal segment of the small intestine and, normal intestinal motility (especially Migrating Motor Complexes) which prevents stagnant activity to prohibit the attachment of ingested organisms within the intestinal lumen. Other factors include; immunoglobulins which provides adequate mucosal immunity, the ileocecal valve, and the secretion of

digestive enzymes by the pancreatic and billiary systems (DiBaise 2008; Syed 2014).

Migrating Motor Complexes (MMC'S) usually occur between meals, i.e. they are interdigestive. For obvious reasons, MMC's more often occur at night. They result from migrating electrical complexes which cause regular pressure changes within the wall of the stomach and small intestine.

The Myenteric plexus generate the MMC's, however, many hormones including motilin also play an important role in MMC initiation and propagation. MMC's are replaced by peristalsis and segmenting waves during a meal but may persist if a meal is light. They can start anywhere in the small intestine and travel distally down the GI tract.

Their role is important in preventing SIBO by mechanically moving debris and bacteria distally, and lubricating the stomach and small intestine. This is particular to phase III of the MMC cycle which comprises of an uninterrupted band of regular contractions which occurs in the small intestine at a rate of 10-12 min. These are forceful contractions which move the intestinal contents distally. This phase lasts between 2-12 minutes and occurs every 90-120 minutes between meals (DLGIP 2009).

A very early study by Vantrappen *et al* (1977) suggested that disorders of the interdigestive motor complex may be an important factor in the pathogenesis of bacterial colonisation in the small intestine (Vantrappen *et al* 1977). Another study by Stotzeer and associates, demonstrated that patients with SIBO lack interdigestive phase III activity in the small intestine and gastric antrum but have a higher motility index in the distal part of the duodenum. This may be a compensatory increase in motility in the distal intestine (Stotzeer *et al* 1996). Motility dysfunction post GI surgery is a common complication due to autonomic nervous dysfunction and GI hormone disruptions leading to a disruption in the MMC activity (Mochiki *et al* 2007).

GI Surgery that alters and affects the anatomy of the small intestine has commonly been associated with SIBO (Zaidel and Lin 2003). Other conditions related to the development of SIBO include:

Stasis (Anatomic):

• Small Bowel Diverticula

• Surgical e.g. resections, ileal bypass, surgically created blind loops

• Intestinal strictures

• Crohn's disease

• Radiation

• Fistulae (Zaidel and Lin 2003; Vanderhoof and Pauley-Hunter 2013b)

Functional Factors

• Intestinal dysmotility syndromes e.g. MMC dysfunction

• Achlorhydria

• Autonomic neuropathy

• Reduction of gut associated lymphoid tissue (DiBaise 2008)

Miscellaneous

• Cirrhosis

• Acid supressing medications, e.g. proton pump inihibitors, H_2 receptor antagonists

• Pancreatitis

• Immune deficiency

• Antimotility medications

• Radiation enteritis

• Diabetes mellitus

• Short bowel syndrome

• Advanced age (DiBaise 2008; Zaidel and Lin 2003)

Patients with Diabetes Mellitus (DM) may suffer from impaired gastrointestinal motility and/or gastroparesis. Therefore, DM may be a condition associated with the development of SIBO. This is because poorly controlled and long-standing diabetes can injure the enteric nervous system leading to impaired GI motility (Dukowicz *et al* 2007).

Medications such as antidepressants and opiates can disturb the motility in the intestine because of their effect on muscles and nerves (Right Diagnosis 2014). Other medications that affect the motility in the GI tract include anticholinergic agents, adsorbents and absorbents. The mechanism of action of the antimotility agents is to reduce and slow the motility and peristalsis in the small and large intestine (CueFLASH 2014).

Small intestinal bacterial overgrowth is more common in the elderly population because of the onset of new diseases (e.g. diabetes), dietary changes, decreased immune function and reduction in gastric acid, and decreased intestinal motility. This may be caused by the consumption of a large number of medications that contribute to hypomotility (Syed 2014; Dukowicz *et al* 2007). A number of studies have compared the prevalence of SIBO in older adults compared with control groups. Parlesak *et al* showed that SIBO tends to be more prevalent (15.6%) in older patients (61-94 years of age) than in healthy controls (5.9%, 24-59 years of age); however there was variability in their methodology of testing (Parlesak *et al* 2003). Teo M. *et al* (2004) reported that SIBO was identified in 48% of patients in a prospective study looking as the possible cause of chronic diarrhoea (Teo *et al* 2004).

Abnormal laboratory findings are usually only seen in patients with complex or severe SIBO. There may also be evidence of macrocytic anaemia due to malabsorption of vitamin B12 and the presence of faecal fat. These laboratory findings may include a decrease in thiamine and nicotinamide levels as well

as an increase in serum folate and vitamin K levels (Vanderhoof and Pauley-Hunter 2013b). These findings are not diagnostic features of SIBO but are supportive of the diagnosis.

Similarly, endoscopic findings are usually normal in patients with SIBO, however in severe cases where colitis and ileitis occurs; inflammation may be seen during endoscopic examination (Vanderhoof and Pauley-Hunter 2013b).

If diarrhoea is present, stool testing may be performed to see if the cause of the diarrhoea is due to fat malabsorption, inflammation/infection or an osmotic or secretary cause. If faecal fat is present in the stool, fat malabsorption which may result from SIBO, celiac disease or fat maldigestion (e.g. pancreatic insufficiency, chronic pancreatitis) is indicated (Vanderhoof and Pauley-Hunter 2013b). An osmotic gap can be calculated by measuring stool electrolytes and osmolarity. A gap of >50 mosm indicates osmotic diarrhoea which is associated with the ingestion of a poorly absorbed substrate such as fructose. A small osmotic gap and a stool weight of > 1kg/day (volume>1 L/day) indicates secretory diarrhoea (Fan and Sellin 2009).

4.2 Benefits of colonic bacteria

Intestinal microflora provides an important role in metabolic and protective functions for the host. In terms of protective function, for example, the microbes assist in preventing pathogens potentially invading the intestinal mucosa by inhibiting attachment and subsequent entry of such pathogens into epithelial cells. Important metabolic functions include the fermentation of nondigestible carbohydrates such as starches, cellulose and pectins (large polysaccharides) and some oligosaccharides that avoided digestion, all of which provide energy to the colon (Canny and McCormick 2008).

Colonic microbiotas perform numerous functions that benefit the digestive process. These functions include; the production of micronutrients, the metabolism and/or activation of medications, and the biotransformation of bile salts. These microbiota are also involved in the fermentation of indigestible polysacchairdes, and the prevention of luminal colonization by pathogenic microorganisms as mentioned above (DiBaise 2008).

Evidence suggests that fibre degradation occurs in the colon. As there are no fibre enzymes, fibre enters the caecum in its unchanged state. The colonic bacteria ferment the fibre to short chain fatty acids, the most important of these are acetate, propionate and butyrate. The major source of energy for colonic epithelium (colonocyte) comes from butyrate (Chapman 2001).

Bifidobacteria (major group of saccharolytic bacteria), makes up approximately 25% of the total bacterial population. It has many health benefits including, lowering blood cholesterol levels, reducing blood ammonia levels, producing vitamins such as B vitamins, folic acid and digestive enzymes such as casein, and lysozyme. It inhibits the growth of potential pathogens and promotes immune function against malignant cells (Gibson and Roberfroid 1995).

Intestinal bacteria also play a role in the enterohepatic circulation by producing enzymes which deconjugate bile acids in the colon allowing some reabsorption of bile across the intestinal wall (Sherwood 1996). Most however are eliminated in the faeces.

Colonic bacteria can cause both beneficial and harmful effects to the host. Normal flora balance discourages infection by exogenous pathogens and overgrowth of pathogenic organisms by the production of antimicrobial substances or short chain fatty acids by resident flora, which inhibits the growth of these pathogens. Therefore antibiotics that reduce the intestinal flora can disrupt this balance and may result in infections or pathologic overgrowth (Sherwood 1996).

Microflora in the colon also aids in the excretion process of various toxic substances and the flora has also been shown to stimulate immune function through Peyer's patches and gut-associated lymphoid tissue. Disturbances in immune function can be associated with intestinal diseases such as Ulcerative colitis and Crohn's disease (Mai and Morris 2004).

4.3 Consequences of Small Intestinal Bacterial Overgrowth

One of the major effects of SIBO is the undesirable inflammatory epithelial changes that may result in the dampening of villi, damage to the brush border, and the altered cytokines/mediators which affects the absorption process (DiBaise 2008). Normally, in the colon, the epithelial cells and microflora form a barrier that protects the intestine from pathogen invasion. Impairment of this barrier may result in inflammatory disease see Figure 4-2 (Canny and McCormick 2008).

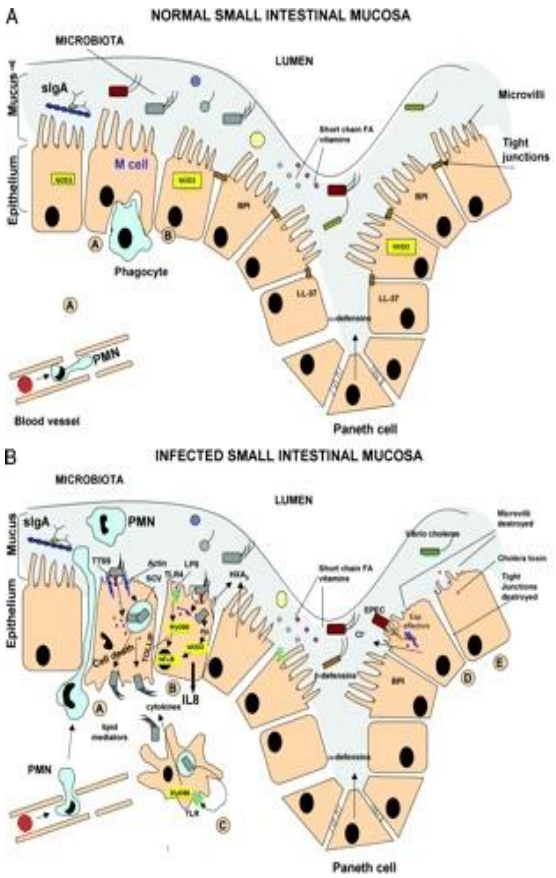

Figure 4-2 - Epithelial Barrier

(Canny and McCormick 2008)

Malabsorption of fats is another consequence of SIBO, this occurs because of bile acid deconjugation by intraluminal bacteria which – in turn, affects micelle formation. A significant concentration of conjugated bile acid is required for the formation of these micelles which transport the fat molecules across the intestinal lumen. Therefore, SIBO indirectly damages the absorptive mucosa and can lead to chronic diarrhoea which is secondary to poor fat digestion and absorption (Zaidel and Lin 2003). Chronic diarrhoea is defined as greater than 3 stools a day for at least four weeks (Teo *et al* 2004). Protein and carbohydrate malabsorption as well as fat malabsorption may also be impaired as a result of bile acid deconjugation. This is as a result of substances such as lithocholic acid being produced which exerts a toxic effect on the intestinal epithelium (DiBaise 2008).

Anaerobic bacterial utilization of Vitamin B12 within the intestinal lumen may result in a deficiency in this vitamin and lead to megaloblastic anaemia. Subsequently the bacterial synthesis may lead to an elevation in folate levels (DiBaise 2008). Other vitamin deficiencies may also arise as a consequence of SIBO and impaired micelle formation and includes deficiencies in fat-soluble vitamins such as vitamin A (e.g. night blindness), D (osteomalacia, tetany), E and K (prolonged prothrombin times) this however is a rare occurrence (Dukowicz *et al* 2007).

Most importantly, SIBO can very often affect the patient symptomatically. This can be both quite uncomfortable for the patient and can affect their lifestyle and/or quality of life. Symptoms are produced as a result of by-products released by the bacteria when they compete with the natural digestive process and metabolise, particularly carbohydrates, within the lumen of the small intestine. Gases such as Hydrogen, Methane and Carbon Dioxide and short-chain fatty acids are produced. These gases can move in both an antegrade and retrograde direction through the GI tract and cause non-specific GI symptoms such as nausea, abdominal/epigastric discomfort, flatulence and abdominal distension. A large amount of CO_2 remains in the small intestine and leads to bloating. In fact, these symptoms can often mimic Irritable Bowel Syndrome (IBS). Malabsorption of fat and poor fat digestion

can lead to steatorrhoea and fat soluble vitamin deficiencies. Diarrhoea can also result from the short-chain fatty acid by-products. This is because they exert an osmotic effect and absorb water into the intestinal lumen (Ledochowski M and Ledochowski E 2008). Some patients with SIBO however may be asymptomatic (Vanderhoof and Pauley-Hunter 2013a).

In addition, the type of bacteria present plays a role in the manifestations of signs and symptoms of SIBO. For example, a predominance of microbial flora that deconjugate bile acid may lead to fat malabsorption or bile acid diarrhoea, while bacteria that prefer to metabolise carbohydrates to short chain fatty acids and gas may cause bloating (Dukowicz *et al* 2007).

Methane slows down gut transit and may cause constipation (less than 3 stools per week). In contrast, it has been shown that excess hydrogen production is linked to chronic non-specific diarrhoea and higher stool frequency (Kumar *et al* 2010). A study by Kumar S. *et al* showed that the production of methane seems to be much more common in control groups than in patients with IBS. This might explain the bloating symptom which is so frequent amongst IBS suffers since 4 atoms of hydrogen combine to produce 1 molecule of methane (Kumar *et al* 2010).

Another complication of SIBO which has been demonstrated in rats is bacterial translocation. This is where the bacteria move from the intestinal lumen across the mucosal barrier which can lead to the appearance of the bacteria in the mesenteric lymph nodes and visceral organs. This may lead to the complication of immune response activation and could be related to immune mediated disorders such as fibromyalgia, interstitial cystitis, and chronic fatigue syndrome (Petrone *et al* 2011).

D-lactic acidosis can occur due to bacterial overgrowth metabolising carbohydrates leading to excess production of D-lactic acid. The clinical presentation is characterised by recurrent episodes of unusual neurological manifestations and severe metabolic acidosis (Zhang *et al* 2003). Common features include slurred speech, memory loss and confusion especially after

high carbohydrate meals (Emmett 2013). In severe cases, colitis and ileitis can occur which may be evident on endoscopy. This inflammation can mimic a flare of Crohn's Disease (Vanderhoof and Pauley-Hunter 2013a).

4.4 Small Intestinal Bacterial Overgrowth Following Surgery

After surgery, the presence of adhesions may play a role in intestinal stasis and contribute to SIBO (Petrone *et al* 2011). A study by Petrone P. *et al* showed that in a group of 57 patients who were tested for SIBO, 45 patients had a positive result. Of these 45 patients, 82% had a history of abdominal surgery. They also found in their study that the mean age of SIBO patients was higher than that of SIBO-negative patients (57 vs 44 years). The surgery performed on this patient group was both laparoscopic and open surgery. The most frequent surgery was on the female reproductive organs (64%) followed by the hindgut, foregut and midgut (Petrone *et al* 2011).

Small intestinal bacterial overgrowth following a gastrectomy is quite common because of complex reconstructions and pouches. One of the reported reasons is due to the loss of gastric acid, while another reason is the formation of blind-loops (Griffin and Raimes 2007). Impaired intestinal motility, reduction in gastric acid and disrupted immunologic secretions are also thought to contribute to the development of SIBO. Steatorrhoea and megablastic anaemia are the most common clinical features. It is estimated that dumping syndrome can occur in 15-50% of patients following oesophageal and gastric surgery.

Paik *et al* examined a total of 77 patients for bacterial overgrowth post-gastrectomy using a hydrogen-methane glucose breath test and they also performed simultaneous dumping syndrome questionnaires, serum glucose, hematocrit and pulse rate measurements. The prevalence of dumping syndrome in this study was 46.1%. Following the ingestion of glucose, samples were taken every 10 minutes up to 2 hours. A positive study was interpreted as an increase in hydrogen or methane concentration of >12ppm above baseline. Of those patients that were found to be positive (77.6%) for SIBO, 73.7% had an increase of >12ppm by the 50 minute mark and all 59 patients (77.6%) by the 60th minute. At the 20 minutes interval post ingestion

of glucose, the cumulative positivity appeared and reached plateau at 60 minutes.

Only 1 (1.7%) patient was positive for SIBO by methane measurement only. This study also found no difference in positive and negative studies regarding patient age, gender, time of testing post-surgery, type of gastric surgery, and the presence of dumping syndrome. This was also the case for BMI and laboratory data for nutritional status. It was noted in this paper that false positive results due to rapid intestinal transit should be considered. However, the study pointed out that even if the cut-off point for positivity was at the 30 minute increment, 52.6% of patients would still have tested positive for SIBO (Paik *et al* 2011).

4.5 Management of Small Intestinal Bacterial Overgrowth

Intestinal Stasis, when not associated with surgical conditions, should be corrected where possible e.g. the elimination or substitution of certain drugs known to decrease intestinal motility i.e. narcotics, benzodiazepines. In other cases where intestinal motility may need to be increased, prokinetic agents may help in this instance but it is not known how much of a benefit they have in aiding the treatment of patients positive for SIBO. To induce Phase III of the migrating motor complex (described in Section 2.1), Octreotide may be prescribed (Vanderhoof and Pauley-Hunter 2013a). Post antibiotic therapy, a low dose of erythromycin may be prescribed. This antibiotic has hormone properties which stimulates small intestinal peristalsis (SIG 2014; Ohio GI 2014).

In the management of SIBO, nutritional intervention and support plays an important role. For those with diagnosed or suspected SIBO, it is quite common in clinical practice to prescribe an antibiotic regime to reduce the bacterial overgrowth and reverse mucosal inflammation associated with SIBO (Dukowicz *et al* 2007). This regime will be discussed in further detail in Section 4.6.

Supplements to counteract micronutrient deficiencies may be required in addition to short term diet restriction i.e. fat restriction to reduce steatorrhoea. It may be necessary to have a diet that consists of nutrients which are readily absorbed in the intestine, thereby leaving fewer calories for bacterial metabolism (Vanderhoof and Pauley-Hunter 2013a).

As mentioned above, excessive or prolonged acid suppression may or may not be a contributing factor. In those patients where proton pump inhibitors (PPI's) are suspected to be associated with the development of symptoms caused by SIBO, a reduction in PPI and/or lifestyle changes to control gastric

reflux may be recommended. However, the effects of PPI's on HBT results remain controversial (Dukowicz *et al* 2007).

In severe cases where other management strategies have failed, surgery may be considered in those patients who have significant weight loss and diarrhoea. This may include postoperative repair of strictures and blind loops, intestinal tapering procedures and intestinal transplant. It may also include surgical correction of strictures, fistulae and diverticula (Vanderhoof and Pauley-Hunter 2013a; Syed 2014). The primary goal is to reduce the bacterial overgrowth rather than total eradication of protective microorganisms with antibiotics therapy (Syed 2014). Pharmacological components may be prescribed in combination with the antibiotic therapy to improve and enhance/restore small intestinal motility.

In cases where the underlying aetiology causing SIBO is unknown, additional tests should be performed e.g. imaging of the small bowel to rule out anatomical causes of SIBO such as intestinal dilations, diverticulitis, fistulae, or strictures. In those with more than two episodes of SIBO with negative imaging and endoscopies, magnetic resonance cholangiopancreatography (MRCP) may be considered to rule out chronic pancreatitis (Vanderhoof and Pauley-Hunter 2013b).

4.6 Antibiotic Regime

Currently, St. James's Hospital regimen for treatment of SIBO is rifaximin 400mg QDS for 7 days. This is given as first line antibiotic therapy to reduce the bacterial flora levels within the small intestine.

Most patients respond well to appropriate antibiotic therapy (Shelly *et al* 2009). Because of the diverse nature of the organism, therapy providing coverage for both aerobic and anaerobic organisms is recommended (DiBaise 2008). Examples include:

1) Amoxicillin-clavulinic acid (30mg/kg/day)

2) Metronidazole (20mg/kg/day) combined with a cephalosporin (30mg/kg/day).

3) Norfloxacin (800mg/day)

4) Rifaximin (1650mg/per day) (Vanderhoof and Pauley-Hunter 2013a).

The antibiotic rifaximin is poorly absorbed and has shown to be effective when treating patients who were positive for SIBO using glucose substrate when compared to Chlortetracycline [(70% vs 27% respectively) (DiBaise 2008)]. Rifaximin treats infections only in the intestine. It passes through the stomach and into the intestine without being absorbed into the blood stream. Clinical resistance tends to be less than with other antibiotics (Vanderhoof and Pauley-Hunter 2013a). Another study by Vanderhoof (2013) reported in their literature review that 69% of patients treated with rifaximin had a clinical response compared with other non-rifaximin antibiotics (Vanderhoof and Pauley-Hunter 2013a). In contrast, a randomised trial comparing rifaximin and metronidazole recommended the benefits and use of metronidazole for treating SIBO and associated symptoms (Dukowicz *et al* 2007).

Nucrea *et al* suggested treating patients with a one week course of either rifaximin, metronidazole or fluroquinolines. In their study of 64 patients who were treated for SIBO, 40 (62%) showed normalization of their lactulose HBT following antibiotic therapy (Nucera *et al* 2005).

The duration and dosing regimen of the antibiotic therapy for rifaximin varied amongst studies and reports. Some suggest a one week course, some a 7-10 day course while others recommend a two week course of the antibiotic (Nucera *et al* 2005; Petrone *et al* 2011; Vanderhoof and Pauley-Hunter 2013a; Dukowicz *et al* 2007). Variations in the dosage of rifaximin have also been subject to controversy. Some institutions believe that 550mg bd is sufficient to treat SIBO (Andreyev *et al* 2014). It has been suggested that some patients may require prolonged therapy of one to two months before a response is seen and symptoms improve. Patients with recurrent symptoms may require continuous or cyclical antibiotic therapy i.e. first 5-10 days of every month (Syed 2014). Recurrence is common after treatment and tends to be in older adults with chronic PPI use (Vanderhoof and Pauley-Hunter 2013a; Lauritano *et al* 2008).

The use of probiotic therapy to treat SIBO has been the subject of diverse opinions. Outcomes using probiotic therapy is inconclusive and not generally recommended (Syed 2014).

Chapter 5

5 Methodology

5.1 Method of physiological measurement

At rest and while appropriately fasting, humans do not exhale hydrogen, it is generated as a result of anaerobic metabolism (Eisenmann *et al* 2008). When Hydrogen is produced as a by-product of bacterial metabolism, it is readily and quickly absorbed across the lumen of the intestine (Simren and Stotzer 2006). The gas enters the circulatory system and travels in the normal systemic flow towards the respiratory system. Here, the hydrogen gas is expired along with other gases through alveolar exchange. It is this expired hydrogen gas that is measured using the HBT device (Gastro+ Operating Manual 2014).

Both glucose and lactulose are the substrates most commonly used for detecting SIBO. Lactulose is in some circumstances preferred as it travels the length of the small intestine and therefore has the ability to detect SIBO in the more distal parts of the small intestine. As a synthetic disaccharide, it cannot be metabolised into monosaccharides and absorbed as there is no naturally occurring lactulose enzyme present to perform this biological function. Therefore, the lactulose travels intact to the colon where it is metabolised by colonic bacteria. By this means, orocaecal transit time can be measured. In rare instances, there are bacteria present in the colon which are unable to breakdown the synthetic lactulose into fructose and galactose but these bacteria are still capable of producing hydrogen (Eisenmann *et al* 2008).

Glucose in general, is the most popular choice for detecting SIBO. It is readily absorbed and is a more sensitive substrate. The sensitivity and specificity of the lactulose HBT in detecting SIBO has been reported to be only 68% and 44% and for glucose HBT 62% and 83% (Simren and Stotzer 2006). There are also a number of limitations to using lactulose substrate that may result in false positive and false negative results (see Section 5.2).

The glucose HBT can also been used in other applications such as in patients suffering from pancreatic insufficiency where it was shown be positive for SIBO in 40% of patients. This was also the case in patients with liver cirrhosis where up to 33% were found to be positive for SIBO (Eisenmann *et al* 2008). In the Gastrointestinal unit, St. James's Hospital, the HBT is also used to test for lactose malabsorption, fructose malabsorption, and sucrose malabsorption. The dose concentration of the solution consumed and the length of time it takes to perform these procedures differs to that of the SIBO test. The HBT is a simple technique to perform, inexpensive, non-invasive, does not have any side effects, has several applications, and multiple studies can be performed using the one HBT device at the same time.

5.2 Values for detecting Small Intestinal Bacterial Overgrowth

The fasting baseline of expired hydrogen should be <10ppm (ideally <5ppm). A high baseline may suggest slow intestinal transit whereby residual food is still being metabolised or it may be due to the presence of SIBO. This however is quite uncommon and is more than likely due to poor adherence of the pre-procedure protocol to avoid high fibre foods the day prior to the HBT.

The glucose hydrogen breath test is considered positive if there is a clear peak in measured hydrogen. Again, there is vast variability amongst users as to what is the normal cut-off point. A majority of studies suggest that a hydrogen peak exceeding 10-20ppm above baseline is indicative of a positive glucose test (Simren and Stotzer 2006). While others suggest that any increase over 10ppm above baseline is considered significant (Eisenmann *et al* 2008; Croagh *et al* 2007). In our unit, we recommend that a rise of >12ppm above baseline is indicative of SIBO, refer to Figure 5-1. Some other studies suggest a similar protocol (Vanderhoof and Pauley-Hunter 2013b; Dukowicz *et al* 2007).

Small intestinal bacterial overgrowth detection using lactulose is measured by observing for a ‘double-peak’. An initial early peak of >12ppm within the first 60 minutes followed by a larger peak indicating that the lactulose solution has reached the colon, refer to Figure 5-2 (DLGIP 2009). There are limitations to this measurement. For example, it may be difficult to distinguish SIBO from colonic fermentation if there is rapid transit and the effect of lactulose itself must be considered as it increases intestinal transit. The detection of two distinguishable peaks may also result in false positives if an initial bolus reaches the caecum imitating the first peak before the rest of the luminal contents reach the caecum producing the second peak (Simren and Stotzer 2006). Normally lactulose reaches the colon within 70-90 minutes (Eisenmann *et al* 2008).

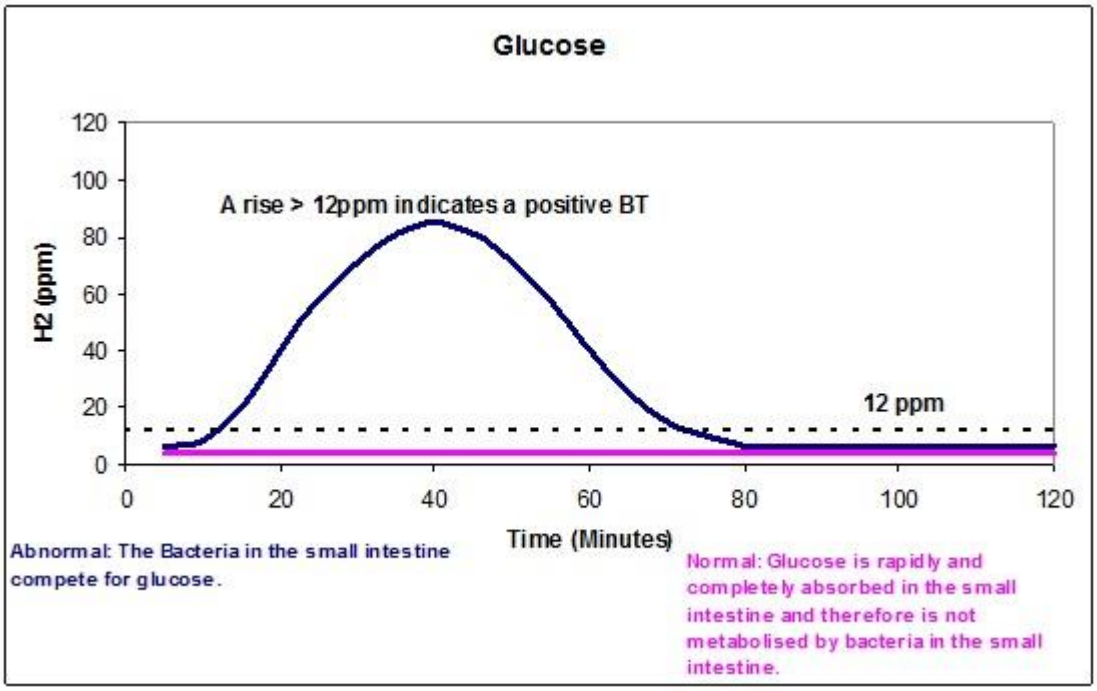

Figure 5-1 - Normal and abnormal HBT using glucose substrate

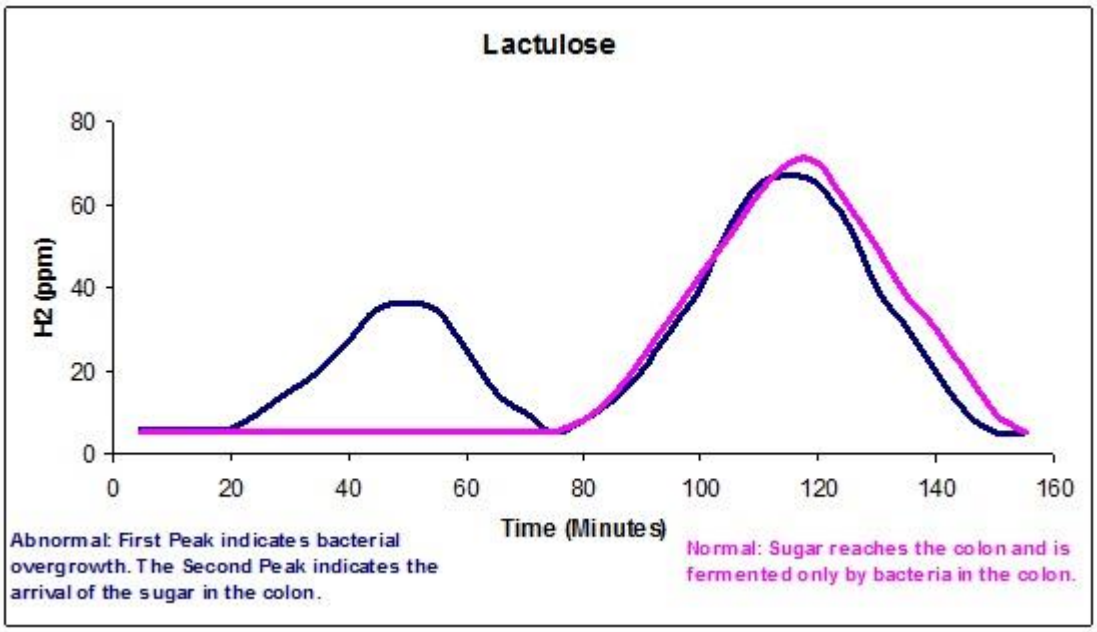

Figure 5-2 - Normal and abnormal 'ideal' HBT using lactulose solution

5.3 Factors affecting Hydrogen Breath Test analysis

Smoking and exercise are restricted before and during the study. Smoking has the effect of raising the hydrogen concentrations while exercise lowers the concentration of hydrogen measured (Simren and Stotzer 2006).

False negative results may occur in patients with gastrointestinal motor disorders e.g. delayed gastric emptying in which case, the HBT may be concluded before the substrate had the chance to reach the intestine. In contrast, those with rapid transit through the small intestine may yield a false positive result due to metabolism of the substrate by colonic bacteria. This is because of the reduction in the time frame where the substrate makes contact with the absorption mucosa. Subsequently, it is then transported to the colon where metabolism occurs.

With regards with malabsorption studies as opposed to SIBO, there are several addition potential errors that may exist in addition to those listed above. These include patients that suffer from chronic pancreatitis and coeliac disease (Simren and Stotzer 2006). This is because the release of enzymes from the intestinal source is compromised leading to the inability of disaccharides to be broken down into monosaccharides and therefore an absorbable form.

The use of fructose as a substrate may be unreliable and difficult to interpret. Fructose is found in many everyday foods and beverages as a sweetener. It is also present in fruits such as apples, peaches, cherries and pears. Absorptive capacity of fructose by carrier mediated facilitated diffusion varies greatly and tends to be dose and concentration dependant. When fructose is ingested with glucose, the absorption of fructose increases. However, when fructose is ingested with sorbitol, the absorption of fructose decreases. In dietary sources, both glucose and sorbitol are more likely to be found in combination with fructose. Therefore, HBT using fructose alone does not reflect the normal

dietary consumption of fructose ingestion (Simren and Stotzer 2006). Some units use 50g of fructose dissolved in 250mls of water, but this does not correspond to real physiological situations nor does it make a difference in the results if 25g was used instead. In addition to this, it may lead to more side effects during the study (Eisenmann *et al* 2008).

5.4 Limitations in Hydrogen Breath Test

Glucose tends to be more sensitive in detecting SIBO compared to lactulose solution. However, some argue that because glucose is absorbed in the proximal part of the small intestine, SIBO investigation may result in a false negative result. Lactulose on the other hand is a synthetic sugar and therefore not absorbed. It travels distally, intact, to the colon where it is metabolised by colonic bacteria. Therefore the lactulose solution travels the entire length of the small intestine and in addition, has the ability to measure orocaecal transit time.

A lack of hydrogen production can occur due to a predominance of intestinal bacteria which metabolise hydrogen themselves. Some bacteria produce methane from hydrogen (Dukowicz *et al* 2007). Bacteria that can contribute to a lack of hydrogen production include; acetogenic bacteria, methanogenic bacteria, nitrate-reducing bacteria, sulphate-reducing bacteria or it can be as a result from the lack of hydrogen producing bacteria within the colonic lumen (Ledochowski M and Ledochowski E 2008).

The analysis of methane gas can identify SIBO is those patients who are not hydrogen producers. Methane breath testing can identify approximately 10% more patients with SIBO when compared to the glucose hydrogen breath test alone (Rusu *et al* 2012).

HBT using fructose substrate is absolutely contraindicated in those with known or suspected hereditary fructose intolerance or in those with postprandial hypoglycaemia (Eisenmann *et al* 2008).

5.5 Gastro+ Gastrolyzer® measuring system

The Gastro+ Gastrolyzer ® (Figure 5-3) is intended for multi-patient use in a clinical setting. The monitor is configured by uploading the patient's data via a USB port connected to a PC which has the GastroCHART PC software installed. The device has a colour touch screen display and allows the user to view results in a list or graphical configuration. It requires three AA alkaline batteries to power the device.

Figure 5-3 - Gastro+ Gastrolyzer® measuring system

(Gastro+ Operating Manual 2014)

The Gastro+ must be switched on in fresh air to ensure an accurate zero level. It is turned on by holding the on/off button until the display lights up and becomes active. The unit will automatically power off after 45 minutes of inactivity. A D-piece is then inserted into the slot on the device, Figure 5-4. This D-piece is a one-way valve to prevent air being drawn back into the monitor. The air passes through an infection control filter that removes and traps >99.9% of airborne bacteria. It should be changed once a month or when visibly soiled as it cannot be cleaned or sterilised. Between breath tests, the D-piece should be removed to allow fresh air to circulate around the hydrogen sensor (Gastro+ Operating Manual 2014).

Figure 5-4 - D-piece

(Gastro+ Operating Manual 2014)

Figure 5-5 - Disposable mouthpiece

(Gastro+ Operating Manual 2014)

A single-use disposable cardboard mouthpiece is then slotted over the D-piece and the connections firmly checked, Figure 5-5. The procedure is then ready to be carried out according to the guidelines in Section 5.6.

5.6 Hydrogen Breath Test procedure

The patients arrive to the GI Function Unit for SIBO investigations following a strict 12hr fast. No antibiotics are permitted for at least four weeks before the study and no colonoscopy should be performed at least one month prior to this study. This is because of the reduction in the normal bacterial flora levels in the colon.

Avoidance of high fibre foods the day prior to the test is another requirement because these high fibre foods can cause prolonged hydrogen secretion and elevate basal measurements (Vanderhoof and Pauley-Hunter 2013b). Other food products that are also not advised include onions, leeks, garlic, cabbage, beans or any pickled vegetable (Ledochowski M and Ledochowski E 2008). Laxatives, in particular lactulose should be discontinued for at least 3 days before HBT (Eisenmann et al 2008). Smoking and chewing gum should be discontinued for 12hrs prior to study. Antimotility drugs are discontinued for two days prior to the HBT.

The patient is asked to perform a preliminary mouth wash with a chlorhexadine agent before a baseline breath sample is taken. This is to ensure that oral bacteria do not cause false positive results and early elevated measurements of expired hydrogen. The baseline breath sample should be 0ppm, but a baseline of up to 10ppm is considered adequate to continue with the study (ideally <5ppm). If the baseline is >10ppm, it might be suggested that the patient returns for their HBT on a subsequent day and follows a 16 hour fast. But this is quite dependant on individual cases and circumstances.

Following the baseline sample, the patient then ingests the appropriate substrate (Table 5-1) and breath samples are taken at 15 minute intervals over a two/three hour period. The data collected is then offloaded from the Gastrolyser to the computer system, printed out and saved accordingly.

Table 5-1 - Dose of substrate and preparation

	Grams	Dissolved
Glucose	50g	In 250 mls hot water and allowed to cool
Fructose	25g	In 250 mls hot water and allowed to cool
Lactulose	10g/15 mls	250 mls of room temperature water

This volume (250 mls) of water is used because if the solution was too concentrated, then there would be a larger non-absorbed proportion which may result in a false positive test. In contrast, the smaller the concentration, the better the absorption rate which may lead to a false negative result (Ledochowski M and Ledochowski E 2008).

Hydrogen is distributed differently depending on the subjects' position (Shelly 2009). During the study, the patient is asked to stay in the sitting position and avoid exercise/walking throughout the investigation as it may hamper collected samples of expired hydrogen. The HBT results are not affected by the presence of other subject in the procedure room (Eisenmann *et al* 2008).

Even though, the HBT is a non-invasive and cost effective test when compared to performing intestinal aspirates, it can be quite labour-intensive with samples taken every 15 minutes over such long durations.

5.7 Hydrogen Breath Test duration and sampling times

Published data on the optimal test duration is limited. A testing duration of 3 hours has being the longest reported time frame when testing for SIBO (Grace *et al* 2012). A study from The Royal Marsden NHS Foundation Trust in London showed that most patients testing positive for SIBO would do so by the 100 minute mark. In this study, samples were taken every 20 minutes and methane gas analysis was also performed (Grace *et al* 2012). Simren and Stotzer (2006) documented that sampling for SIBO is usually every 15 minutes (Simren and Stotzer 2006).

For our investigations, we sampled at 15 minute increments over a two hour period. This was following the protocols of published data and to ensure no critical values of expired hydrogen were missed especially in those patients with altered GI Physiology following upper GI surgery.

5.8 Calibration of the Gastro+ Gastrolyzer®

Calibration should be performed once a month. If the calibration icon is displayed on screen when the device is switched on, calibration is due. The Gastro+ Gastrolyzer® should be calibrated at 21^{o}C (±4^{o}C). If calibrated at lower temperatures, this may result in lower readings and vice versa.

The calibration gas used is 100ppm hydrogen in air. The device must be zeroed in fresh air prior to calibration. The fine control valve (1) on the hydrogen gas cylinder is turned to allow the gas to flow at 0.5 litres per minute, Figure 5-6. The cylinder is connected to the D-piece on the monitor by using calibration connection equipment between the two pieces. To maintain a steady flow of hydrogen at this required rate of flow, the ball in the flow indicator on the gas cylinder is kept at the lower line (2). The ppm value starts to appear on screen.

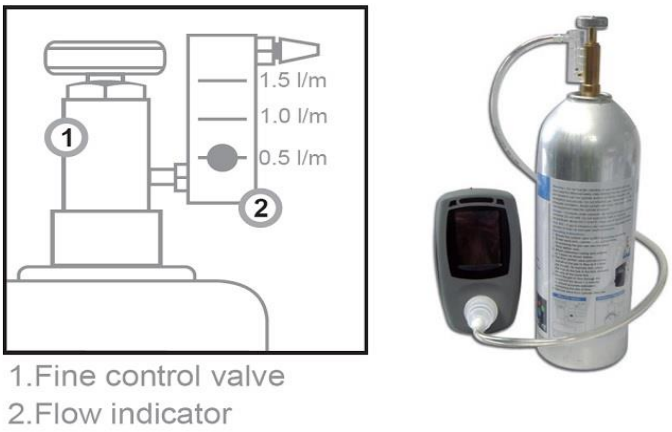

Figure 5-6 - Calibration of HBT device using gas cylinder

(Gastro+ Operating Manual 2014)

If the final ppm reading is between 84-116ppm, the measurement will be accepted and automatically set in the instrument as 100ppm.

5.9 How to exhale efficiently into Gastrolyzer

When a breath sample is taken, the ‘breath’ icon on screen is selected. This initiates a countdown from 15 seconds. The patient is asked to hold their breath based on a resting expiratory position rather than to take a deep breath in (Ledochowski M and Ledochowski E 2008). The patient is asked to continue to hold their breath until further instruction. An audible sound is heard from the monitor for the final 3 seconds of the countdown which is also visible on screen. At the final beep, the patient is asked to insert the mouth piece into their mouth, close lip firmly around the disposable cardboard piece and exhale slowly into the device, Figure 5-7 and Figure 5-8. The patient is encouraged to expel the breath completely from their lungs. The ppm value will appear on the display. This measurement is then saved manually by pressing the ‘save’ icon on screen.

In the case where patients are unable to tolerate the full breath hold, they are asked to inhale and hold their breath for as long as possible and then exhale into the mouth piece as described above.

Figure 5-7 - Screen display during breath sample

(Gastro+ Operating Manual 2014)

A number of patients can be simultaneously tested on this device by uploading all the patients' data via GastroCHART and using the up and down arrows on the monitor to select each patient when taking individual samples. In our unit, we would not recommend performing any more than two simultaneous recordings. The reason for this is because it takes time for the hydrogen measurements to stabilise and this may result in an overlap of timing between patients when sampling every 15 minutes. In addition to this, if each or any of the patients are symptomatic with for example diarrhoea during their study, it would be quite unpleasant for everyone in the clinical area, especially if there are limited toilet facilities available.

Following the last breath sample, the data is then downloaded onto the GastroCHART via a USB cable connected to the PC. The data is displayed in both a graphical and tabular format and lists all the patients' details. The results are then printed and saved on both the local and hospital server in PDF. If the monitor is not likely to be used for some time, it is recommended that the batteries are removed. The hydrogen sensor should be replaced every two years.

Figure 5-8 - Patient exhaling into Hydrogen Breath Test device

5.10 Rational of research and control group

An audit of all referrals for Hydrogen breath testing (HBT) for small intestinal bacterial overgrowth (SIBO) was carried out between 2008-2011. A total number of 194 patients were tested for SIBO using glucose substrate and fructose substrate. Some patients were tested on two different occasions with both solutions. These patients were referred for differing reasons ranging from patients suffering with acute/chronic diarrhoea, steatorrhoea and/or other general abdominal/gastrointestinal disturbances. Patients were also referred post-surgery for an oesophagectomy or gastrectomy who had difficulty gaining weight or malabsorption issues.

A total number of 312 HBT's were performed on these 194 patients (124 female vs. 70 male). Of these, 66 patients were positive (34%) for SIBO using glucose substrate, fructose substrate or having been tested with both solutions. Breath samples were taken at 20 minute intervals in accordance with our unit protocol (during that period) over a duration of up to 2 hours.

The 194 patient cohorts was subdivided into two groups; a group of 22 patients for post Gastrectomy & Oesophagectomy (G & O) and a 172 patient group with diagnosed or suspected Irritable Bowel Syndrome (IBS). Figure 5-9 illustrates a flow chart of this HBT patient audit which took place in the Gastrointestinal function unit, St. James's Hospital between 2008-2011 and their positive HBT results.

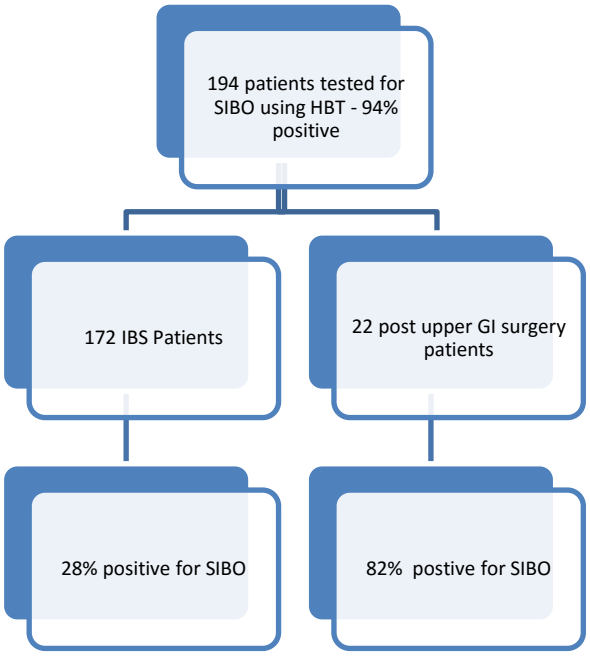

Figure 5-9 – GI Function SIBO Audit 2008 – 2011

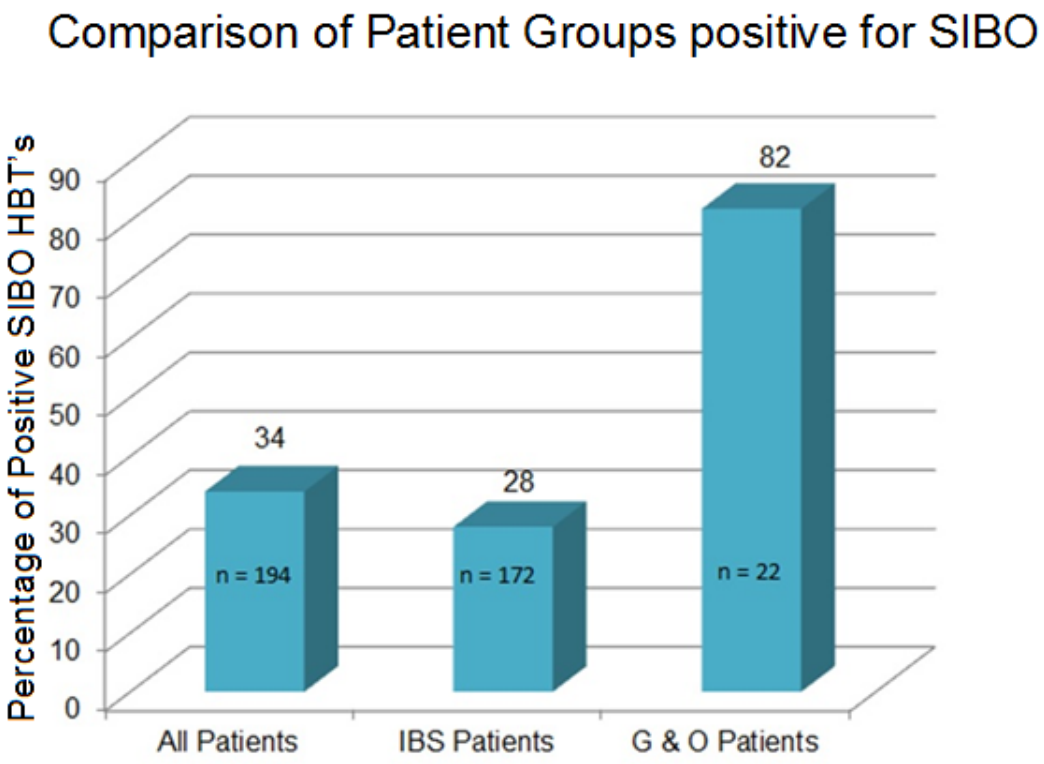

Figure 5-10 - Comparison between patient groups positive for SIBO

The post-surgical group were broken down into oesophagectomy and gastrectomy patients along with their corresponding positive HBT results (refer to table 7.1). We found that 18 out of these 22 patients were positive for SIBO using either glucose or fructose (82%).

Table 5-2 - Post Oesophagectomy/Gastrectomy patients and HBT Results

Surgery Type	No. of patients	Positive	% of Positive SIBO Test
Gastrectomy	7	6	85%
Oesophagectomy	15	12	80%

The glucose or fructose solution used to test for SIBO and the corresponding positive glucose HBT result of this post surgical group of patients is listed in Table 5-3.

Table 5-3 - Post Oesophagectomy/Gastrectomy patients tested for SIBO

Substrate	No. of studies	Positive	Percentage
Glucose	13	7	53%
Fructose	22	17	77%
Both glucose and fructose	9	6	67%

Fructose used in detecting SIBO in post upper GI surgery patients is debatable as the reduced transit time could result in fructose malabsorption being detected as opposed to SIBO. In most literature, glucose is the substrate of choice for detecting SIBO. In the initial research figures below, fructose breath tests were undertaken as the surgical team requested these studies be performed to see if there was a malabsorption issue that was associated with the patients' symptoms. As the research progressed, glucose was requested for SIBO. This was because patients found it too difficult to

attend for both appointments and as fructose has its limitations; glucose was the recommended testing substrate.

A study from the Sheffield Teaching Hospitals NHS Trust showed similar results when they carried out a retrospective analysis of 447 glucose HBT's performed from 1998-2010. These results demonstrated 18.8% positive result for SIBO when measuring both hydrogen and methane in exhaled breath samples (Evans *et al* 2012). This finding was comparable with our data above which showed an 8% positive SIBO finding when testing with glucose substrate (in the 194 patient group above) using hydrogen gas analysis only. In Section 5.4 'limitations of HBT' it mentions that a further 10% of patients may be identified as being positive for SIBO when methane gas analysis is performed in conjunction with exhaled hydrogen.

Based on these HBT audit results which took place in the Gastrointestinal function unit between 2008-2011, a comprehensive research study was initiated to document hydrogen breath test findings in symptomatic patients following an oesophagectomy or gastrectomy. This would include documenting the patients lifestyle habits, type of surgery, cancer morphology, multimodal therapy, Barrett's histology, and post-operative complcations.

5.11 Patient Criteria for researched surgical group

Patients used in this research study were all referred to the GI Function Unit by the Consultant Surgeon to establish the presence of SIBO. All patients referred for HBT in this group received potential curative surgery to treat oesophageal or gastric carcinomas.

The majority of patients referred were symptomatic following their surgery. Chemotherapy and/or Radiotherapy before and/or after surgery was performed in some patients as part of their multimodal treatment plan.

Patients were referred to the unit following their post-surgery clinic appointment. During this clinic visit, the consultant and dietician assessed the patient's progress in terms of their nutritional status and clinical well-being following surgery.

The exclusion criteria for this research group included those patients that:

• Had an oesophagectomy or gastrectomy for reasons which were not related to a malignant tumour e.g. Achalasia

• Had their surgery prior to 2010

• The reconstructive part of the oesophageal or gastric surgery involved a colonic transposition

5.12 Data Collection - Patient Profiles

A new questionnaire was devised by the Gastrointestinal Function Unit for patients attending for their Breath test, refer to Appendix 6. The timing between samples was adjusted to shorter intervals of 15 minutes to reflect the altered GI physiology in this group of patients.

Initially, the main challenge was the co-operation of patients to attend for these tests, as they can each take up to 2hrs to perform. Most of these (68%) patients attending for studies lived outside the catchment area for the Hospital and would have to travel a lengthy distance for their procedures.

Therefore, we co-ordinated where possible, the patients' Hydrogen breath test to be followed by their clinic outpatient and dieticians appointment on the same day. The patients would also receive their results on this day with the surgical team and if necessary, prescribed antibiotics to treat the SIBO.

A total of 106 patients were tested for SIBO post oesophagectomy and gastrectomy. The results of these tests are detailed in Appendix 1

The vast majority of patients in this group, 50% (n = 53) were greater than 66 years of age. Those patients aged 51-65 years represented 37% of this cohort, while those aged between 35-50 years had a 12% presence. Only one patient was younger than 35 years.

Chapter 6

6 Data Analysis & Results

6.1 Hydrogen Breath Test Results

Of the 106 patients referred for this investigation, only 99 patients where included in this study. Two patients had a colonic interposition rather than a gastric conduit as part of their surgery. One patient refused the studies as he found it would be too difficult to fast and travel to the hospital. One patient subsequently passed away, one patient had total dysphagia and was unable to consume the glucose solution, and two patients were non-cancer patients. Of these 99 patients, 60 (61%) had a positive test. The percentage of patients that were positive for SIBO were broken down into those that had an oesophagectomy and those patient that underwent a gastrectomy. Figure 6-1 below lists the number of patients and the corresponding percentage of positive HBT results.

Table 6-1 - SIBO in post gastrectomy and oesophagectomy patients

Surgery Type	No. of patients	Positive	% of Positive SIBO Tests
Gastrectomy	38	20	53%
Oesophagectomy	61	40	66%

The percentage of positive HBT results for SIBO were then analysed by the sugar substrate used for testing in this group of surgical patients. Table 6-2 below shows these findings.

Table 6-2 - Substrate used for SIBO and their positive percentage response

Substrate	No. of studies	Negative	Positive	% of Positive SIBO Tests
Glucose	93	44	49	53%
Fructose	54	26	28	52%
Both glucose and fructose	48	31	17	35%

The timeframe and corresponding positive HBT results of when these patients were tested for SIBO post-surgery was analysed (refer to Table 6-3). Those patients that were tested 7-12 months post-surgery had an 85% positive SIBO result.

Table 6-3 - Duration (months) that patients were tested for SIBO post surgery

Time post op (mths)	No. of studies	Positive	% of Positive SIBO Tests
1-6 mths	59	32	54 %
7-12 mths	27	23	85 %
>1 year	13	5	38 %

6.2 Repeat Hydrogen Breath Tests post Antibiotic Therapy

If the patients obtained a positive result for bacterial overgrowth, the surgical team assessed their clinical response and decided on an appropriate antibiotic therapy for the patient. The patient was prescribed Rifaximin 400mg QDS PO for seven days. A total of 12 patients that were positive for SIBO were prescribed antibiotics and were referred back to the GI unit for re-testing (refer to Table 6-4). Retesting involved having a repeat glucose HBT performed using the same technique as described in section 5.6.

The remaining patients were either treated with antibiotics and clinically assessed for response to therapy rather than a re-test; or not treated with antibiotic therapy because the team recognised a clinical improvement since their last out-patient appointment, (patient felt symptoms are improving and/or patient weight had increased). For these patients, a follow-up clinic appointment for 6/12 months was arranged to re-assess the patient's well-being, and if at this stage the patient's response was deteriorating or symptoms were worsening, then treatment with antibiotics would be considered.

Patients that received antibiotic therapy were sent appointments to return to the GI unit for follow-up retesting approximately 8-10 weeks post antibiotic therapy. To date a total of 12 patients returned for retesting post antibiotic therapy. Nine patients showed a marked improvement in symptoms and had gained some weight.

The patients were retested using the same protocol and timing between samples. Once again, the patient would return to the clinic after their test ended for the team to decide on their treatment, taking into account the patients clinical response, their improvement if any following antibiotic therapy, their retest results and if their weight had increased. Seven patients remained positive post antibiotic therapy, but their ppm value was drastically reduced indicating that there was a response to antibiotic therapy. The results of those patients that were now negative post antibiotic treatment were

analysed according to weather that had underwent an oesophagectomy or gastrectomy (refer to Table 6-5). As these patients showed a marked improvement post therapy, a second dose of antibiotics was not prescribed but the patients were given an appointment to return to the outpatient clinic in 6/12 months for review.

Table 6-4 - Patients retested post antibiotic therapy

Patient No.	Clinical Improvement PA	Retested (mths) PA	Substrate patient retested for	Positive SIBO PA
4	Yes some	7	Glucose, fructose	Yes
5	No	8	Glucose, Fructose	Yes
9	No	7	Glucose, fructose	Yes
17	Yes	2	Glucose x 2, Fructose	Yes first therapy & negative 2nd therapy
24	Yes	2	Glucose, Fructose	No
25	Yes	2	Glucose, Fructose	No
26	Yes	2	Glucose	Yes
27	Yes initially	2 and 10 (one antibiotic)	Glucose, Fructose	Yes on both retests
28	Yes	2	Glucose, Fructose	No
37	Yes	(1)3 weeks , (2) 3mths, (3) 6mths	Fructose, Glucose	Yes first two & negative last repeat
39	Yes, initially	2 and 3 weeks	Glucose x 2 repeats	Yes for both
50	Some then symptoms returned for 2nd repeat	3 months and 2nd repeat 2 months post abx	Glucose	Yes both occasions

PA - Post Antibiotic Therapy. Out of these 12 patients who were retested for SIBO, 5 were now negative for SIBO and 7 patients were still positive for SIBO.

Table 6-5 - % of patients negative for SIBO post antibiotic therapy

Surgery Type	No. of patients	Negative post treatment	% of Positive SIBO Tests
Gastrectomy	4	1	25 %
Oesophagectomy	8	4	50 %
All patients post therapy	12	5	42 %

6.3 Comprehensive breakdown of patient data cohort

A comprehensive analysis was performed to determine whether there were common factors amongst those patients who proved positive for SIBO. A detailed history of the patients treated and their diagnosis was obtained and scrutinised. From this group of 99 patients, 94 patients were studied. The five patients excluded consisted of four patients that were diagnosed with non-cancerous GIST, and one patient that had an oesophagectomy for treatment of Achalasia.

This group of patients that were tested for SIBO post-surgery for an oesophagectomy or gastrectomy as a result of carcinoma were categorised firstly by gender, age at diagnosis, BMI at diagnosis and symptoms experienced at diagnosis as a result of their illness/surgery.

Breath test results for glucose were analysed in this group as it was the substrate that was used in 93% of subjects and is considered to be the gold standard. For purposes of this part of the study as it is quite specific, standardization and comparability of patient data was performed. The data collected is shown in Appendix 2. As mentioned in Section 5.10, the use of fructose in detecting SIBO is debatable; this is because the reduced transit time in this group of patients could result in the rapid emptying of the fructose substrate into the large intestine before it can be absorbed. It could also be as a result of reduced or diminished fructose transport carriers due to intestinal damage/inflammation. This would result in fructose malabsorption as opposed to SIBO. In this instance, we suggested a positive fructose result of SIBO if there was a very early rise in the ppm value. Therefore, it was recommended to the team that only glucose be performed if SIBO is to be examined.

6.3.1 Mean age of group and their associated HBT result

The average age at diagnosis was 63.38 years. This ranged from 34 to 83 years of age. The average age for females at diagnosis was 62.5 years (n = 30) and for males was 63.8 years (n = 64). Those patients that had a positive HBT had a mean age of 62.8 years, while those with a negative HBT had a mean age of 63.94 years.

There were no significant differences in the median age of patients with positive vs negative breath tests. Independent sample Mann Whitney U tests: Age: p=0.812

6.3.2 Symptoms Experienced

There were 266 symptoms in total experienced by this patient group (refer to Figure 6-1). Four of these patients did not experience any symptoms what so ever, their diagnosis was through an incidental finding.

The most common symptom experienced by patients was Dysphagia (n=49), followed by weight loss (n=37). The 'other' symptoms (n=13) experienced by these patients included: chest pain, flank pain, retro-sternal pain, waterbrash, back pain, cough, gastric outlet obstruction, pulsating lump in abdomen, night sweats, and hair loss.

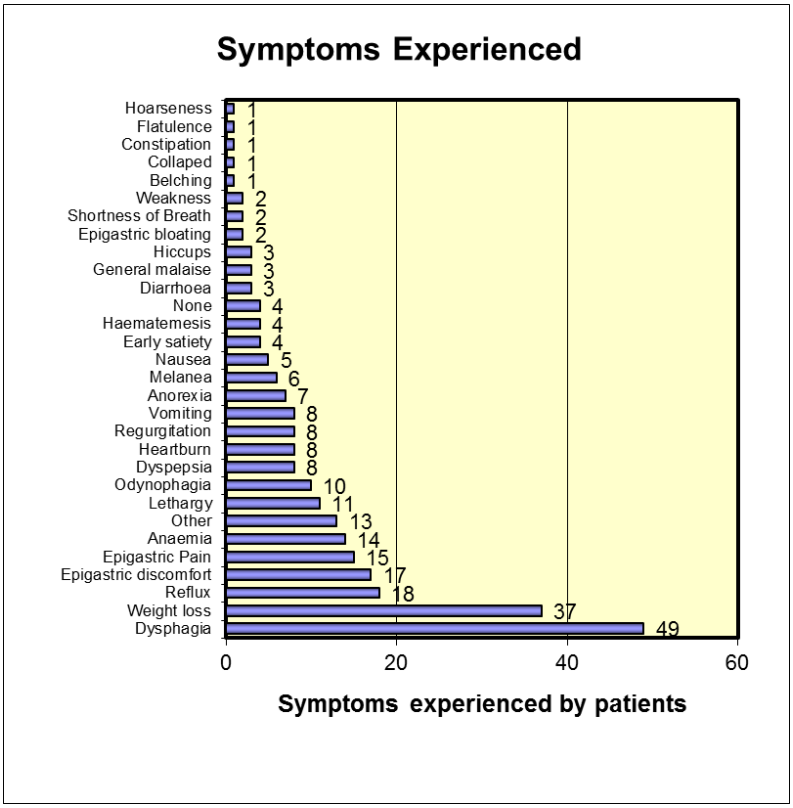

Figure 6-1 - Symptoms Experienced

6.3.3 BMI and Hydrogen Breath Test Result

Some patients (n=19) that were referred from tertiary centres did not have their BMI documented at the time of diagnosis. BMI was documented at the time of diagnosis in the remaining 75 patients (56 males, 19 females). The average BMI in this group was 27.08. The average BMI for females was 24.38 and for males, 28.06.

Normal BMI was marked as being between 18.5-25, overweight 25-30, obese 30+ and the underweight category was reported with a BMI of <18.5. Table 6-6 lists the number of patients in each of these BMI indices and their corresponding positive HBT result.

Table 6-6 - BMI of Patient Group

BMI Index	Females	Males	% of Positive SIBO Tests
<18.5	3	1	5 %
18.5-25	10	16	35 %
25-30	3	18	28 %
>30	4	20	32 %

Out of 75 patients who had their BMI Documented at time of diagnosis, 60% were classified as being overweight or obese. In males alone, 68% were documented at having a BMI of >25. In the female group, 37% had a BMI of >25.

A total of 70 patients with documented BMI had glucose HBT studies performed. Of these patients, Figure 6-2 shows the positive response rate with the corresponding BMI bracket for the combined female and male group.

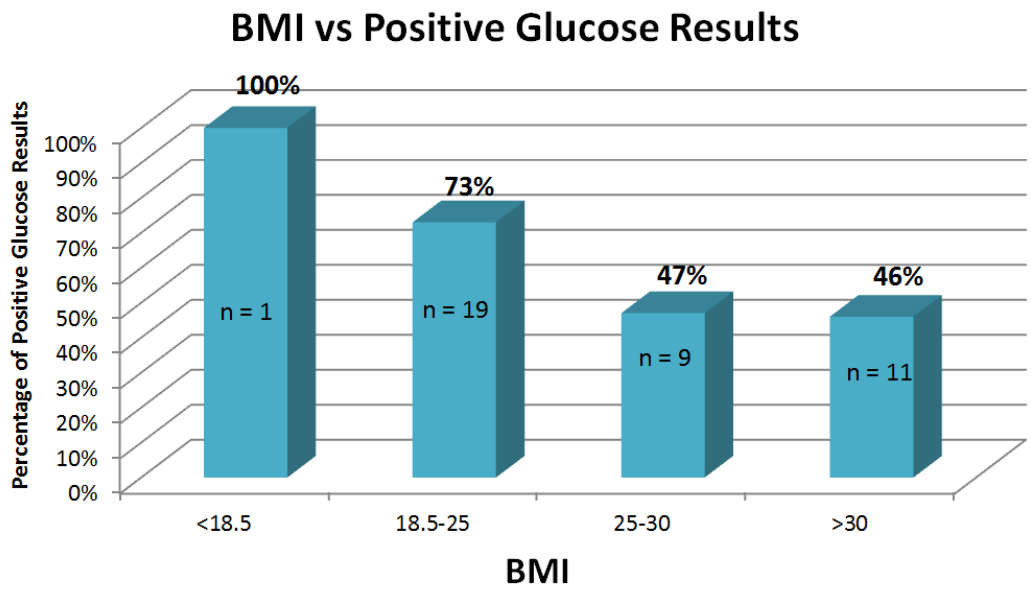

Figure 6-2 - BMI and corresponding glucose result for both female and male group.

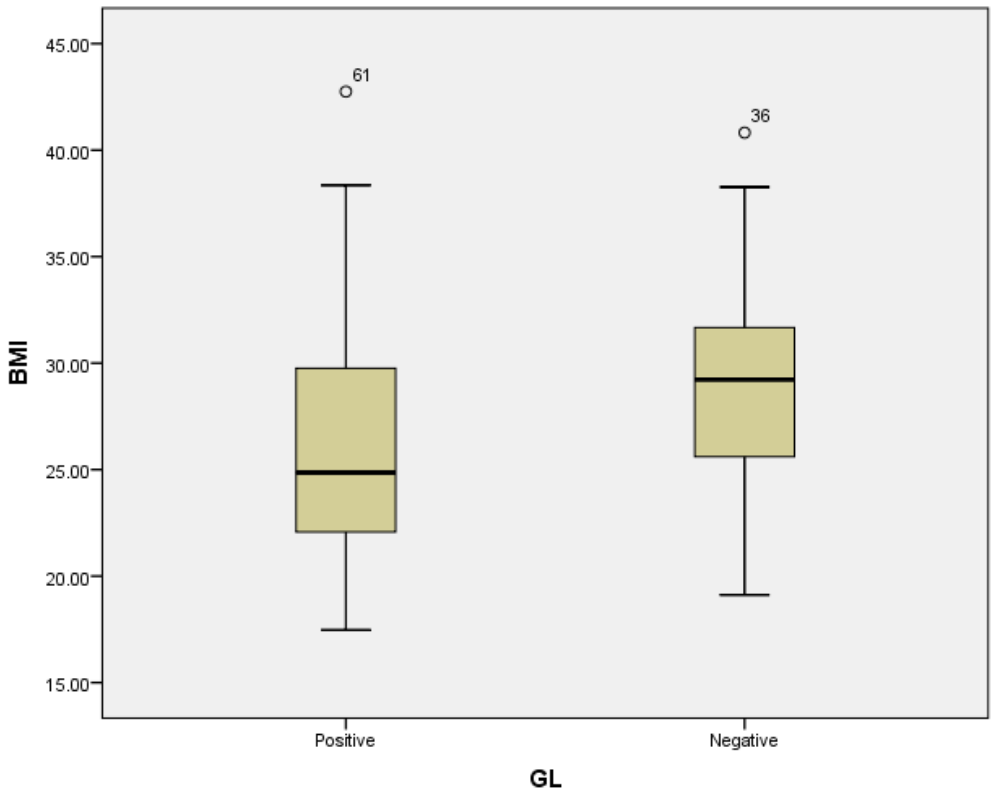

Figure 6-3 - Figure BMI and positive/negative glucose Hydrogen Breath test.

There was no significant difference (Pearsons Chi-square test): 0.067

The median BMI of patients with a positive breath test was 24.86 (range: 17.47-42.75) versus median 29.22 (19.11-40.82) for patients with a negative HBT. This was significantly different (p=0.012, independent samples Mann-Whitney U test).

6.3.4 Smoking and Drinking Habits

Out of these 94 patients, 50 patients were ex-smoker, 15 current smokers, 27 patients never smoked and 2 patient's smoking history were not documented.

Ex-drinkers were documented in 6 patient profiles, 12 patients were heavy drinkers, 59 patients were social drinkers, 14 non-drinkers and 3 patients drinking history were not documented. The number of patients and their smoking and drinking habits is demonstrated in Figure 6-4 below.

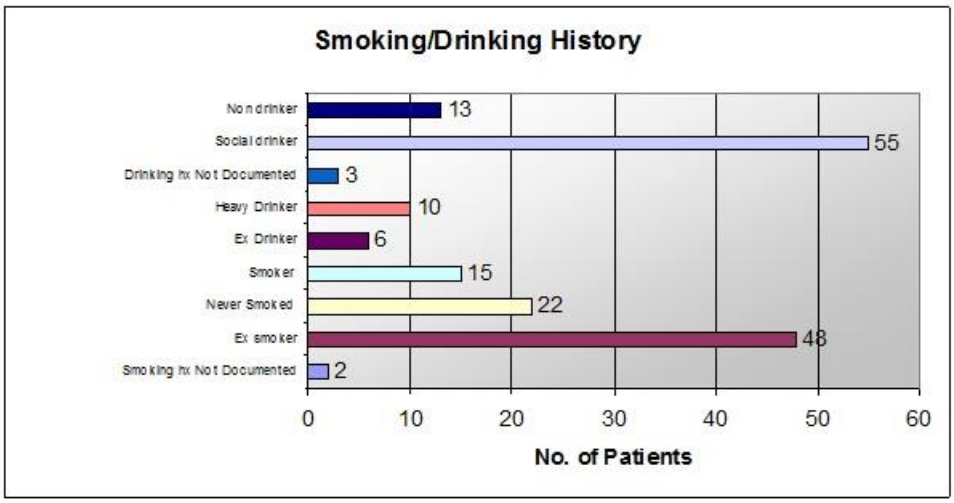

Figure 6-4 - Smoking/Drinking History

Seven patients did not attend for their glucose breath test. These patients were all tested for SIBO using fructose substrate and observed for an early rise in exhaled hydrogen in breath samples. There were varying reasons why these patients did not attend for their glucose breath test including poor health, travelling difficulties, challenges with fasting instructions etc. Therefore, 87 patients were tested for SIBO post major upper GI surgery using glucose substrate.

Out of these 87 (60 males, 27 females) patients who were tested with glucose substrate, 46 patients (53%) were positive for SIBO (refer to Table 6-7).

Table 6-7 - Results of glucose breath test

	Positive Glucose HBT	Negative Glucose HBT
Total	53% (n=46)	47% (n=41)
Male	43% (n=26)	57% (n=34)
Female	74% (n=20)	26% (n=7)

Female patients were significantly more likely to have a positive HBT than male patients (74.1% versus 43.33%, p=0.011).

Ex-smokers dominated this category representing 56% of patients. Of this, ex-smokers had a 42% positive percentage rate. Non-smokers represented 26% of patients and had a 73% positive result for SIBO using glucose substrate. Current smokers, 18% of group, had a 60% positive glucose BT result. Smoking history and the corresponding positive glucose HBT results are shown in Figure 6-5. There were 2 un-documented patient files. Therefore, those patients that never smoked were more likely to have a positive HBT (72.7%) vs. patients who were either current or ex-smokers (46.2%, p=0.047). The odds ratio for those patients that were smokers having a positive HBT versus those patients that never smoked is OR = 0.678 (95% CI; 0.16, 2.85).

The entire ex-smokers group smoked cigarettes only. The average amount of cigarettes smoked per day was 27. This value ranged from 1-100 cigarettes per day. The average amount of years that these patients smoked for was 27.83 years. This ranged from 2 years right through to 50 years of smoking.

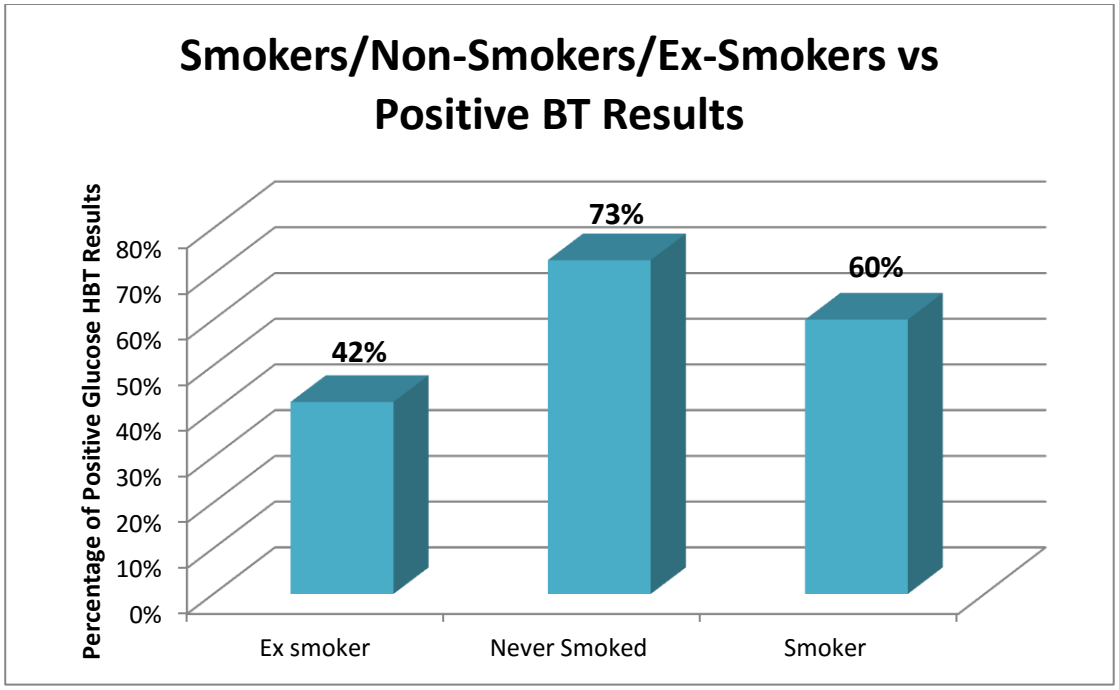

Figure 6-5 - Smokers/Non-Smokers/Ex-Smokers vs Positive BT Results.

The 'Never smoked' group were more likely to have a positive HBT (72.7%) vs. patients who were either current or ex-smokers (46.2%), p=0.047.

Social Drinking was defined by: <14 units per week for females and <21 units per week for males. Social drinkers were highly represented within this group, accounting for 65% of the total. Out of this, 53% had a positive breath result using glucose substrate. Non-drinker totalled 15% of the group and had a positive breath test result of 77%. Next were the 'heavy drinkers' at 12% of the group and had a positive result of 30%. Finally, the 'ex-drinkers' at 7% of the group had a 33% positive breath test result. Drinking habits and the corresponding positive breath test results are shown in Figure 6-6. 'Non-drinkers' were more likely to have a positive HBT (76.9%) vs heavy drinkers (30%), p=0.032. The odds ratio for those patients that were drinkers having a positive HBT versus those patients that were non-drinkers is OR = 0.28 (95% CI; 0.07, 1.12) while the odds ratio for those patients that were heavy drinkers having a positive HBT versus those patients that were social drinkers is OR = 0.48 (95% CI; 0.11, 2.13).

Patients who were documented as being heavy drinkers, consumed up to 50 units of alcohol per week. Those patients who were noted as ‘ex-drinkers’ all had a history of alcohol dependency.

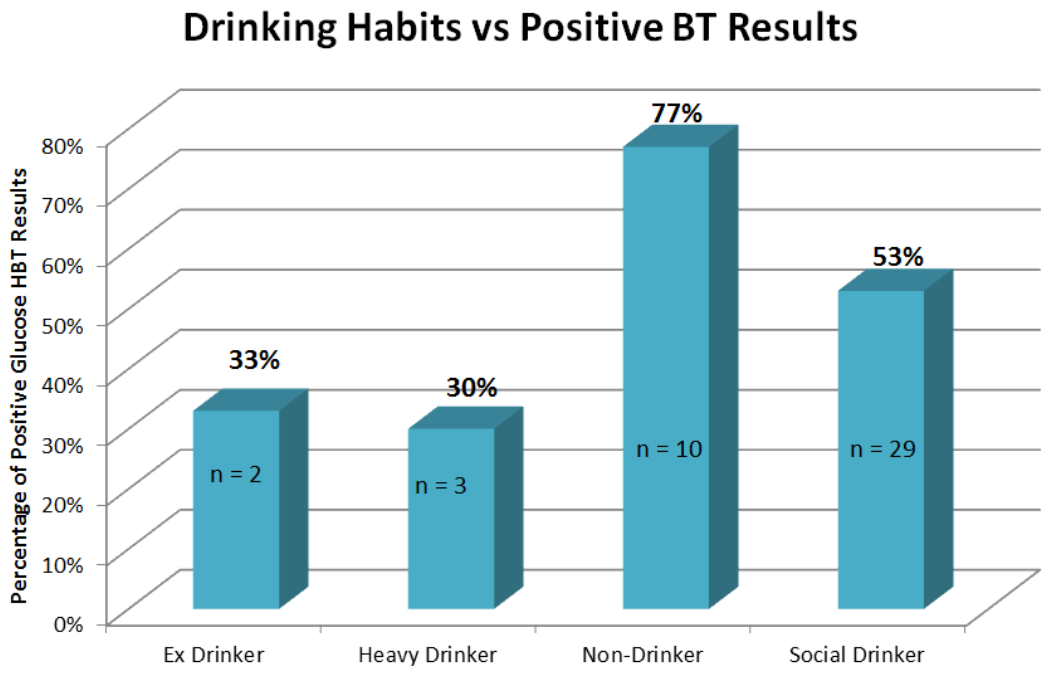

Figure 6-6 - Drinking Habits vs Positive BT results.

Non-drinkers’ were more likely to have a positive HBT (76.9%) vs heavy drinkers (30%), p=0.032

6.3.5 Disease recurrence and malignancy history

Post-Surgery, 11 (13%) patients died as a result of disease recurrence. A further 10 (11%) patients are alive with disease while the remaining 66 (76%) patients have showed no evidence of disease recurrence to date.

Of these 87 patients who were tested for SIBO using Glucose, 64 (74%) patients had no known previous malignancies. Malignancies were documented in 22 (25%) patients (refer to Figure 6-7). One patient's malignancy history was not documented.

Out of these 22 patients who had a previous history of malignancy, ten different cancer types were documented.

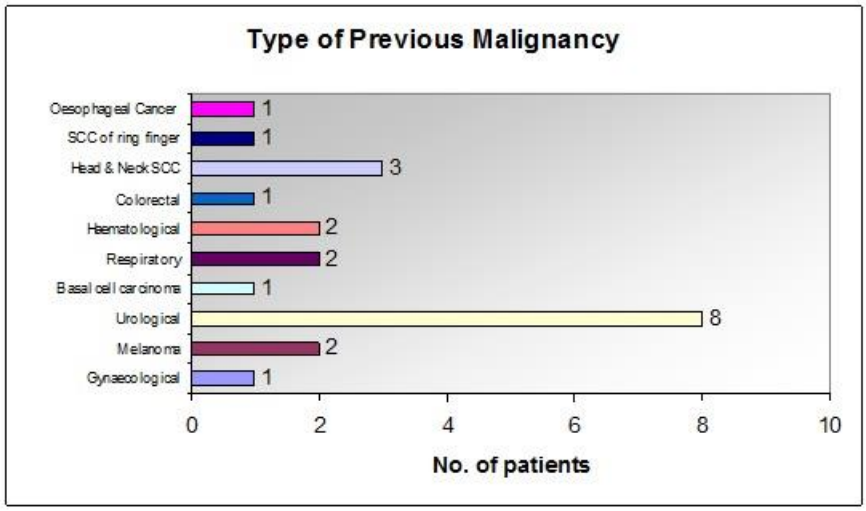

Figure 6-7 - Types of Previous Malignancy

From this group of patients who had a previous history of malignancy, two patients (9%) were documented as currently having disease, while two (9%) morbidity cases were reported from those patients who had a previous cancer diagnosis.

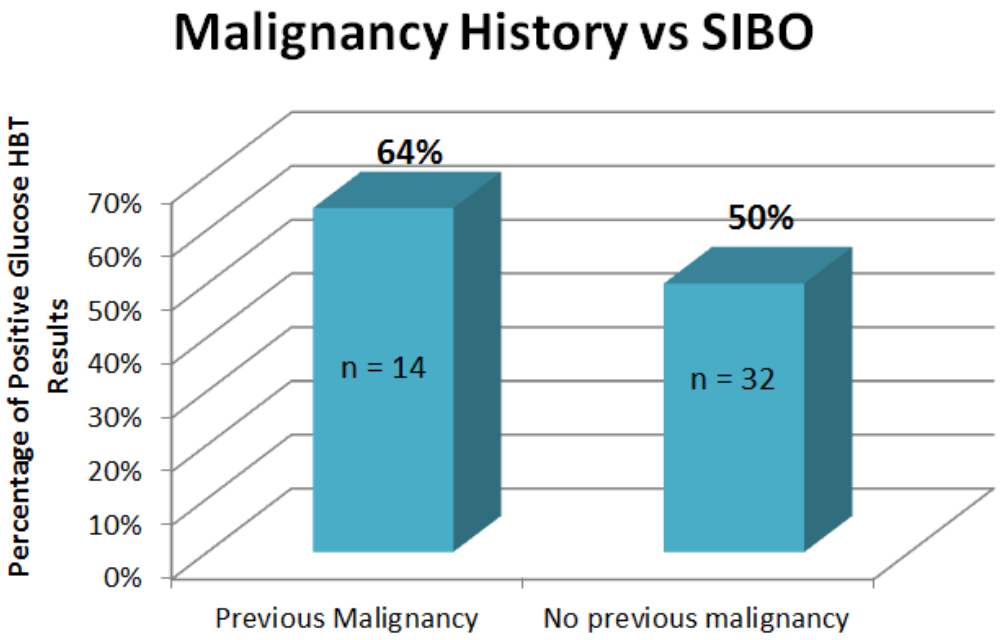

Figure 6-8 - Malignancy History Vs SIBO.

Those patients with a previous history of malignancy (n=22) had a positive glucose breath test of 64% while those without a previous diagnosis of malignance had a positive glucose result of 50%. Malignancy history and the corresponding positive glucose HBT result is shown in Figure 6-8. Patients with a previously diagnosed malignancy were no more likely to have a positive HBT than patients without a history of malignancy (63.3% vs 50%, p=0.326). The odds ratio for those patients that had a history of previous malignancy having a positive HBT versus those patients that had no previous malignancy history is OR = 1.75 (95% CI; 0.65, 4.74).

The majority of patients who had a previous malignancy documented where not GI related.

6.3.6 Barrett's Histology

Barrett's histology was recorded in 67 patients (refer to Figure 6-9). Out of this group, 43 patients had no known Barrett's diagnosed either before or during evaluation of their oesophageal cancer. Patients with known Barrett's oesophagus on diagnosis of cancer, accounted for 19% (n=13) of this group, while 16% of patients were found to have a Barrett's oesophagus when undergoing evaluation for their cancer.

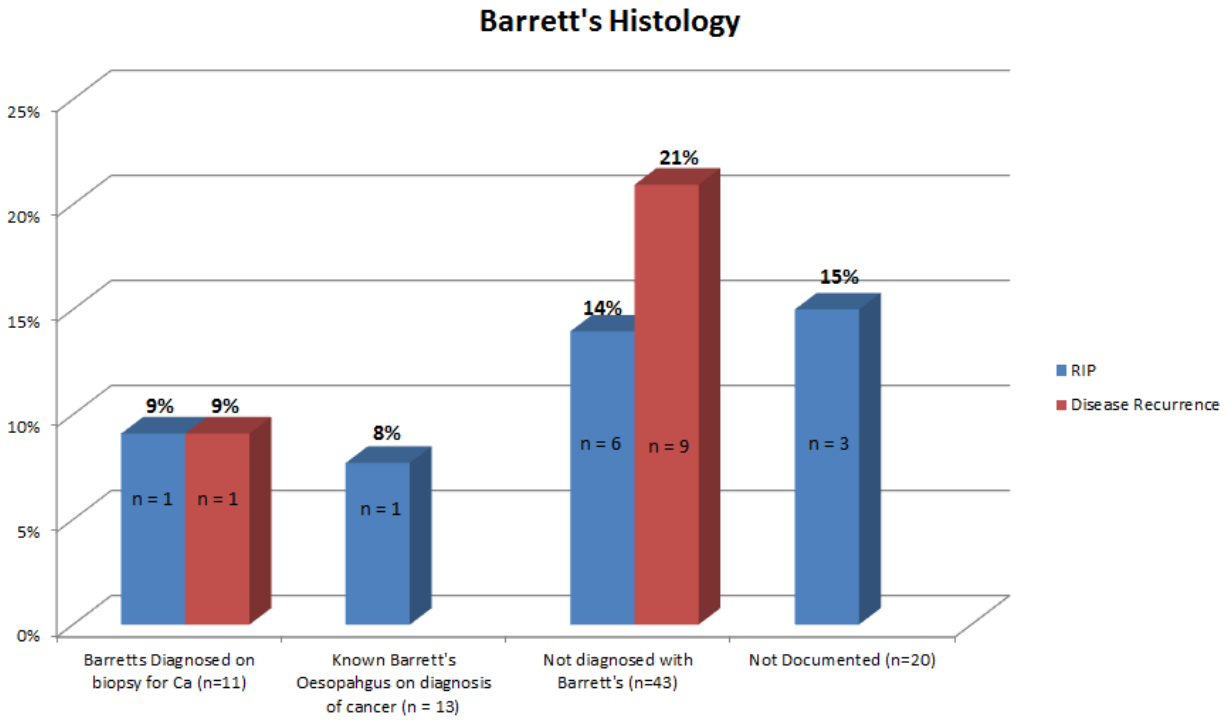

Figure 6-9 - Barrett's Histology

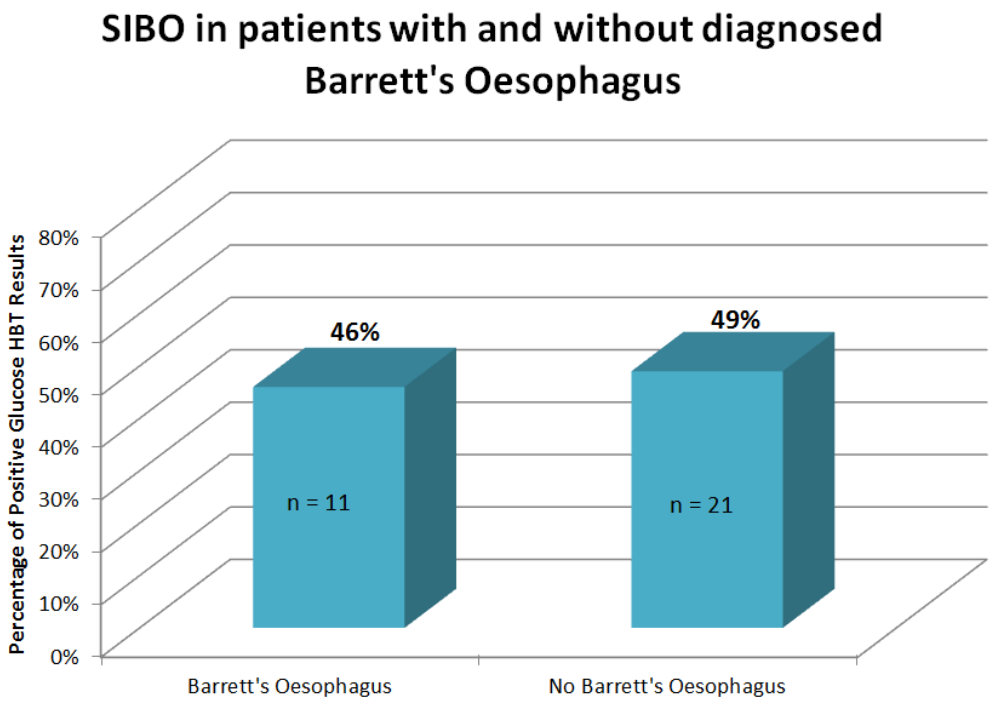

Figure 6-10 - SIBO in patients with and without diagnosed Barrett's Oesophagus

Patients with Barrett's oesophagus were no more likely to have a positive HBT in the post-operative period (45.8% vs 48.8%, p=1.00). The odds ratio for those patients that had documented Barrett's Oesophagus having a positive HBT versus those patients that had no documented Barrett's Oesophagus is OR = 0.89 (95% CI; 0.33, 2.41).

There were 67 patients in total with documented Barrett's histology results. Of those diagnosed with Barrett's oesophagus, 46% were positive for SIBO. Those patients that were documented as not having Barrett's oesophagus showed a 49% positive response for SIBO using glucose substrate. This is demonstrated in figure Figure 6-10 above.

6.3.7 Tumour Site and Morphology

The Oesophageal gastric junction was the most common location of tumour findings and this was the case in 54 patients representing 62% of this group (refer to Figure 6-11). This was followed by tumours located in the mid and distal oesophageal body, accounting for 8% and 9% of the group respectively.

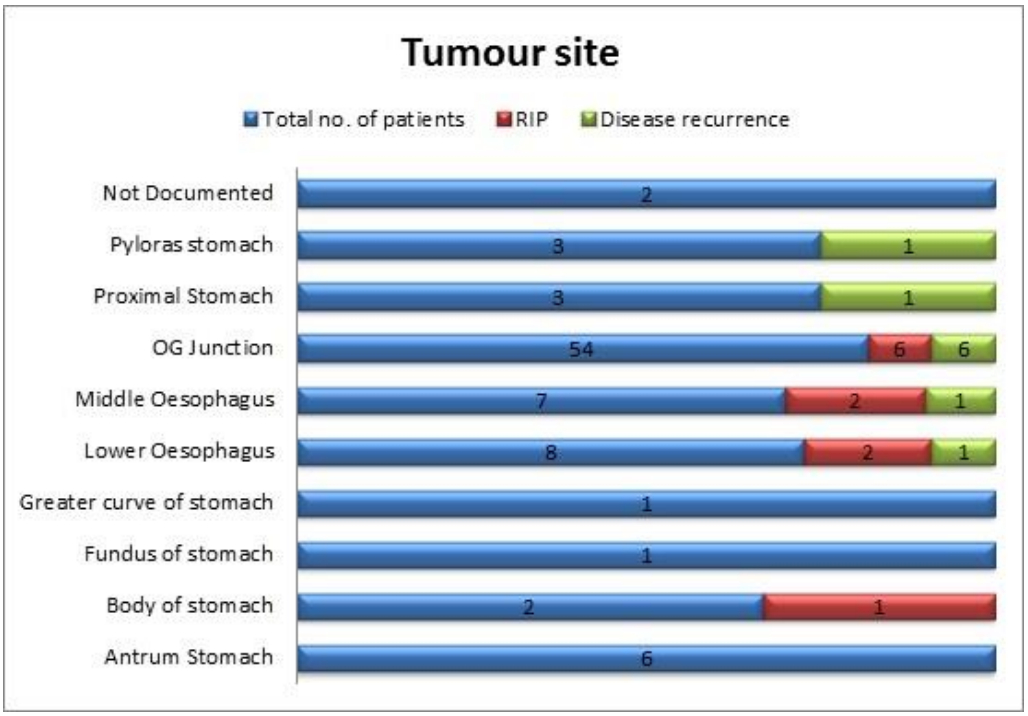

Figure 6-11 - Tumour Site

Adenocarcinoma was diagnosed in 89% of cases (n=76). The morphology was not documented in two cases. Surgery was performed on all 87 patients.

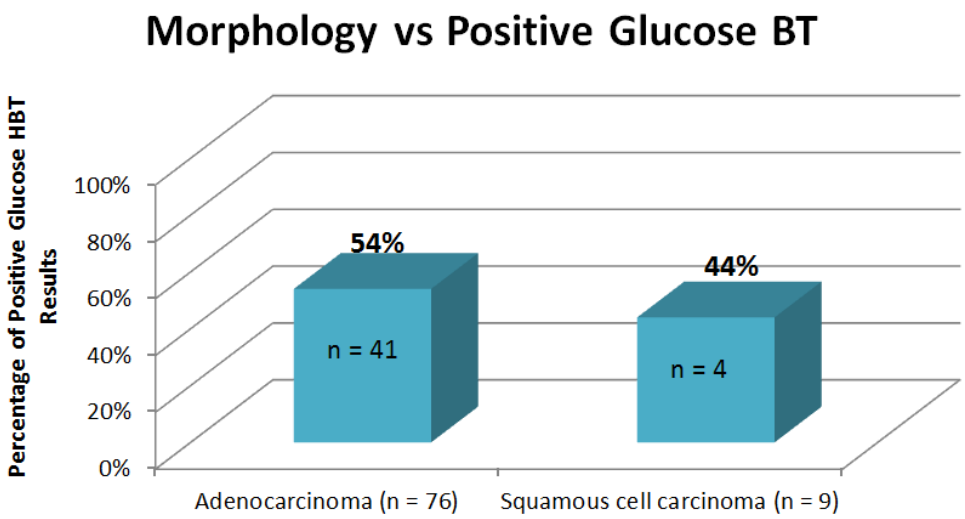

Figure 6-12 - Cancer cell morphology Vs positive glucose study.

The 76 patient group that were documented as having an adenocarcinoma showed a 54% positive result for SIBO. Those patients with diagnosed squamous cell carcinoma displayed a 44% positive result for SIBO (refer to Figure 6-12). There was no significant differences noted according to histological subtype (positive HBT rate in adenocarcinoma vs squamous cell carcinoma: 53.9% versus 44.4%, p=0.729).

6.3.8 Treatment type and intent

Over half of this patient group (51%, n = 44) had both surgery and neo-adjuvant therapy, while 47% (n = 40) had surgery alone as their primary curative treatment. Surgery and adjuvant therapy was performed in 2% (n = 2) of patients from this cohort. One patient who received neo-adjuvant therapy also went on to receive adjuvant therapy.

Most of these surgical cases (95% n = 83) had a curative intent. However, the surgical outcome in 3 (4%) cases was uncertain and in one case it was decided to perform surgery for palliative care. Out of the 3 uncertain cases, 2 patients now show no evidence of disease recurrence while the other patient is alive with disease.

6.3.9 Post Surgery outcomes and complications

The graph shown in Figure 6-13 demonstrates the correlation between the type of oesophageal and gastric surgery and the associated post-surgery complications and breath test results.

Transhiatal oesophagectomy and 2-stage oesophagectomy were the GI surgical procedure that correlated to the highest complications post operatively. Similarly, breath test results in 2-stage (60%) and 3-stage oesophagectomy's (67%) were represented by the highest positive results.

* Since only one patient had undergone a partial gastrectomy, this patient's result is not listed in the top two groups above.

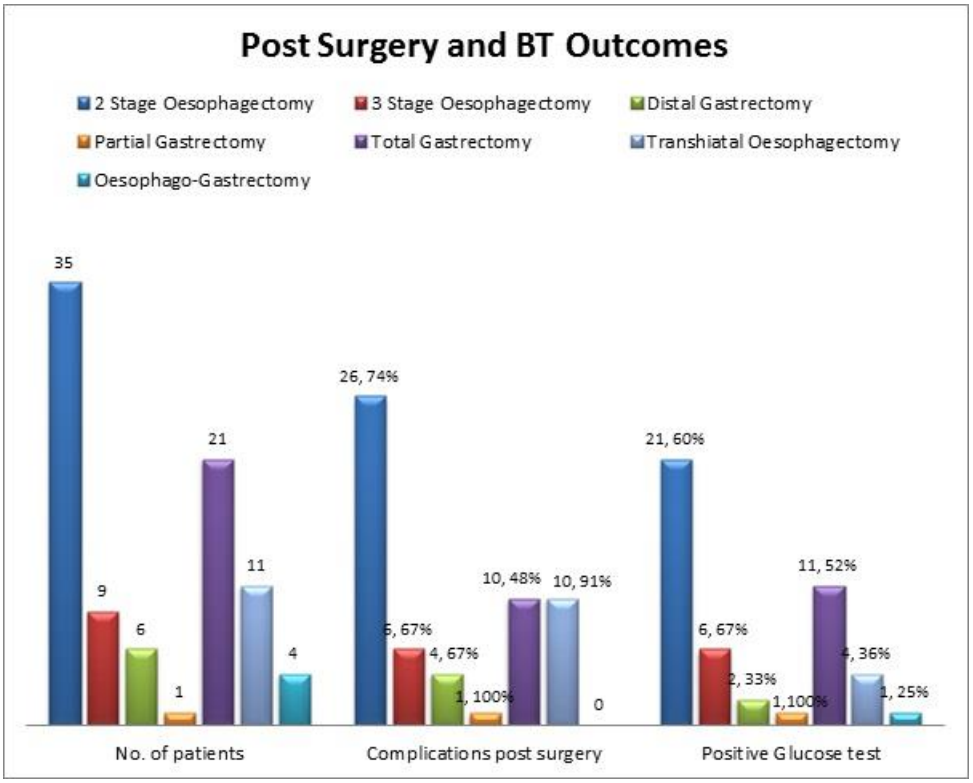

Figure 6-13 - Post Surgery and BT Outcomes

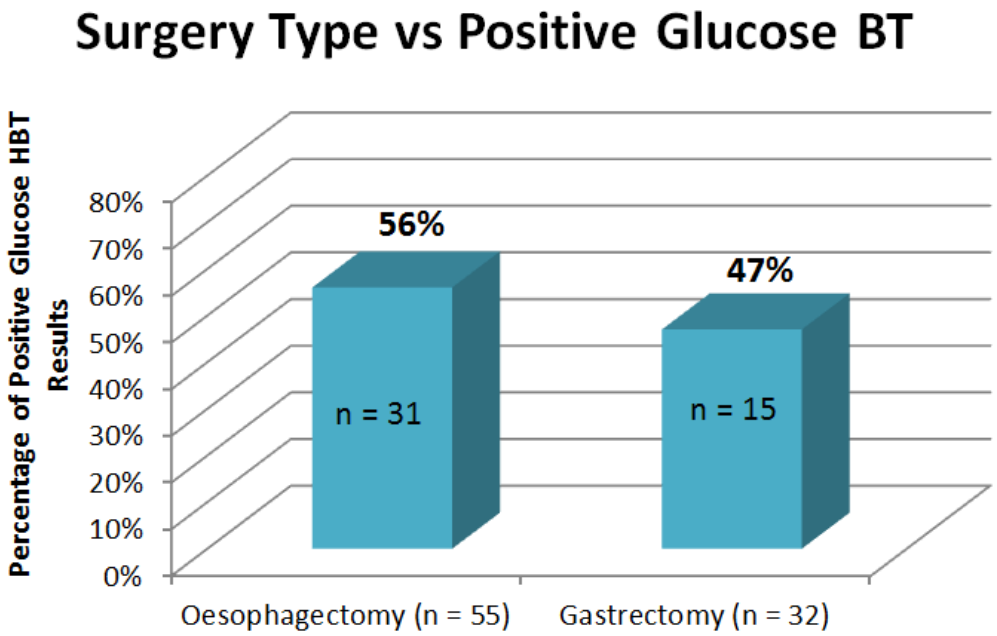

Figure 6-14 - Surgery Type vs Glucose BT.

Figure 6-14 above shows the collective surgical numbers when categorised into oesophagectomy or gastrectomy groupings, and their corresponding positive glucose HBT results. The four patients that were documents as having an Oesophago-Gastrectomy were placed in the gastrectomy group above. Those patients who underwent an oesophagectomy (n=55) showed a 56% positive glucose result while those patients who had a gastrectomy (n=32) performed had a 47% positive glucose result. The proportion of patients who had a positive HBT did not significantly differ whether they had previously had an oesophagectomy versus a gastrectomy, p=0.682.

Complications post operatively occurred in 57 patients. Of these, 5 patients had to return to theatre and 5 patients had a return stay in the High Dependency Unit (HDU) and/or Intensive Care Unit (ICU). The 30 patients who had no recorded complications post operatively had no further theatre or HDU/ICU admissions.

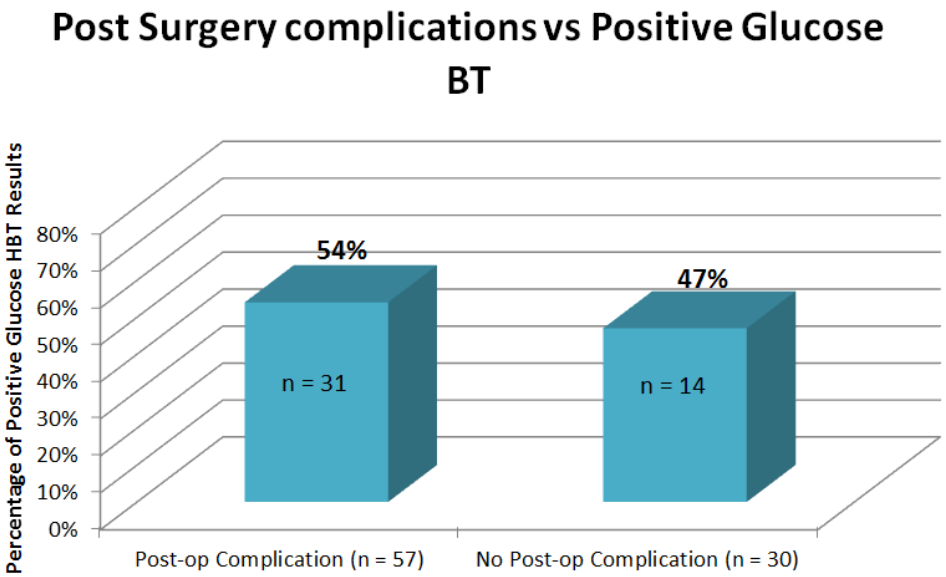

Figure 6-15 - Post – Op complication Vs SIBO detected by HBT

A total of 57 patients suffered from post-surgery complications and of these 54% were positive for SIBO using glucose substrate. SIBO was evident in 47% of patients that did not suffer from any major post-surgery complications (refer to Figure 6-15).

Patient who had post-operative complications were no more likely to have a positive HBT than patients who did not suffer a post-operative complication, p=1.0. The odds ratio for those patients experiencing post-operative complications having a positive HBT versus those patients with no post-operative complications is OR = 1.36 (95% CI; 0.56, 3.31).

Of the 57 patients who had post-op complications, 97 complications were recorded. From this, respiratory infections were the most commonly reported complication (23%). This was followed by cardiac arrhythmias and respiratory failure at 19% and 11% respectively. Figure 6-16 lists the complications experienced in this patient group post-surgery and the number of patients affected by each of these complications.

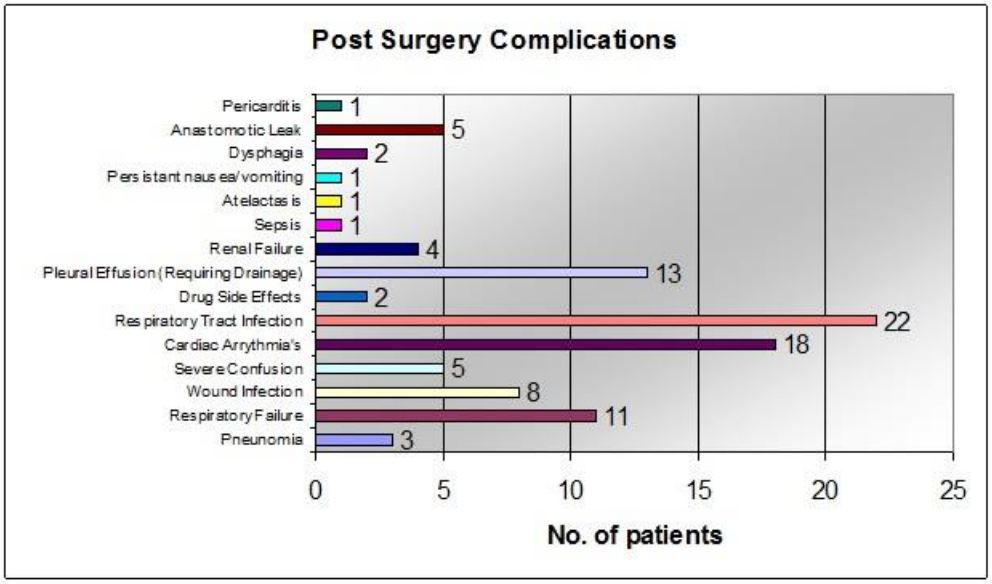

Figure 6-16 - Post Surgery Complications

6.3.10 Chemotherapy and Radiotherapy received

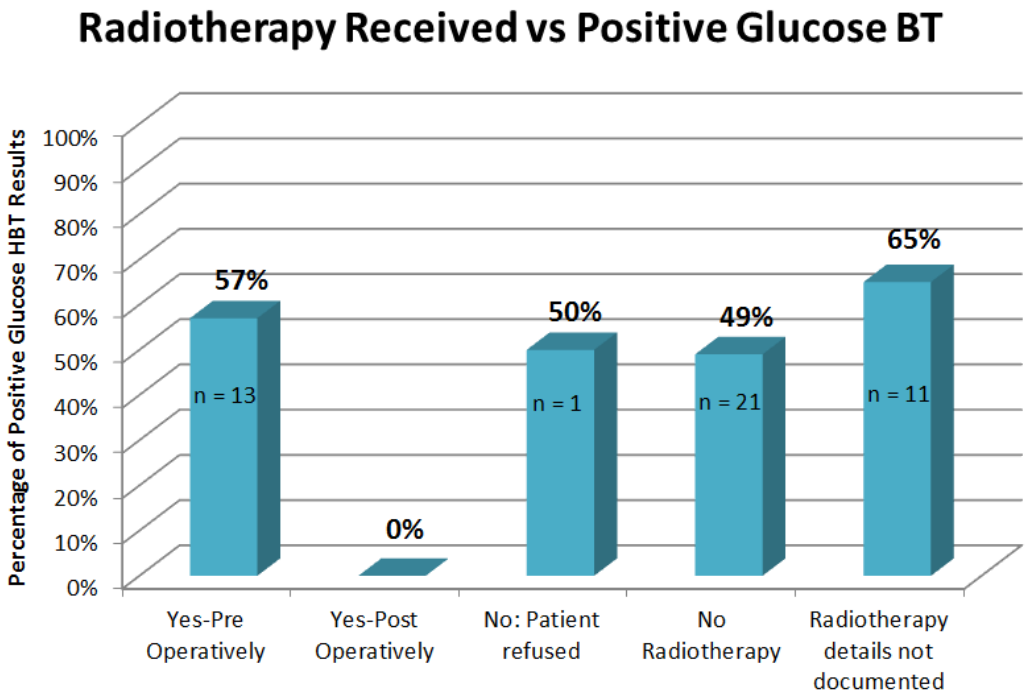

Figure 6-17 - Radiotherapy Received.

Patients who had radiotherapy (52.5% vs 48.9%, p=0.682) were no more likely to have a positive HBT than patients who had surgery alone. The odds ratio for those patients undergoing radiotherapy having a positive HBT versus those patients that had no radiotherapy is OR = 1.13 (95% CI; 0.43, 3.01).

The radiation used in all cases was external beam (electrons) and the dose ranged from 13-45 Gy.

A total of 25 patients were documents as having radiotherapy before and/or post-surgery. Of these, 52% were diagnosed as having SIBO. Those patients that did not receive radiotherapy (n=45) had a 49% positive detection rate for SIBO using glucose substrate. Figure 6-17 displays the radiotherapy treatment received and corresponding positive glucose HBT result.

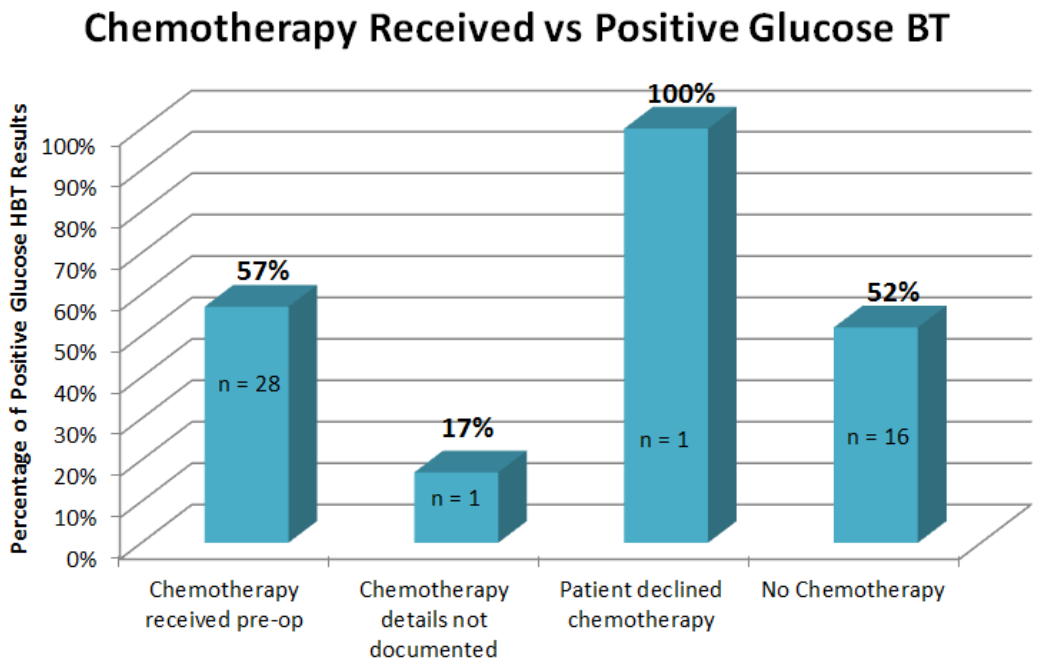

Figure 6-18 - Chemotherapy Received.

Patients who had chemotherapy (57.1% vs 53.1%, p=0.82) were no more likely to have a positive HBT than patients who had surgery alone. The odds ratio for those patients undergoing chemotherapy having a positive HBT versus those patients that had no chemotherapy is OR = 1.18 (95% CI; 0.48, 2.88).

The chemotherapy regime and number of cycles administered varied widely amongst the patients receiving therapy.

A total of 49 patients received chemotherapy prior to their surgery. Of these, 57% were positive for SIBO using glucose substrate. Patients who did not receive any chemotherapy (n =32) showed a 53% positive response to glucose HBT. Those patients that received or did not receive chemotherapy and their corresponding positive glucose HBT results are displayed in Figure 6-18.

Neither patients who had radiotherapy (52.5% vs 48.9%, p=0.682) nor chemotherapy (57.1% vs 53.1%, p=0.82) were more likely to have a positive HBT than patients who had surgery alone.

6.3.11 Post-Surgery Hospital Stay

The length of stay in hospital following surgery varied from 8 to 67 days. As can be noted from Figure 6-19, the longer the length of stay in hospital corresponded to the highest percentage rate of post-op complications e.g. of the 12 patients who were in-patients for 24-27 days, 11 of these were noted to have post-op complications.

The average length of stay was 20.64 days and the median was 17 days stay in hospital following their upper GI Surgery. The standard deviation was 11.718

Similarly, this was the same pattern for the glucose results, as demonstrated in Figure 6-19 and Figure 6-20. The longer the length of stay in hospital post-op, the rate of positive glucose breath tests appeared to increase. However, there were no significant differences in the median length of stay of patients with positive vs negative breath tests. Independent sample Mann Whitney U tests: Length of stay p=0.676

There was no apparent pattern with the association of hospital stay versus type of surgery. However, it was noted that the least days spent in hospital post-op, were occupied by those patients who had a total gastrectomy. These 3 patients spent 8, 9 and 9 days in hospital following their surgery.

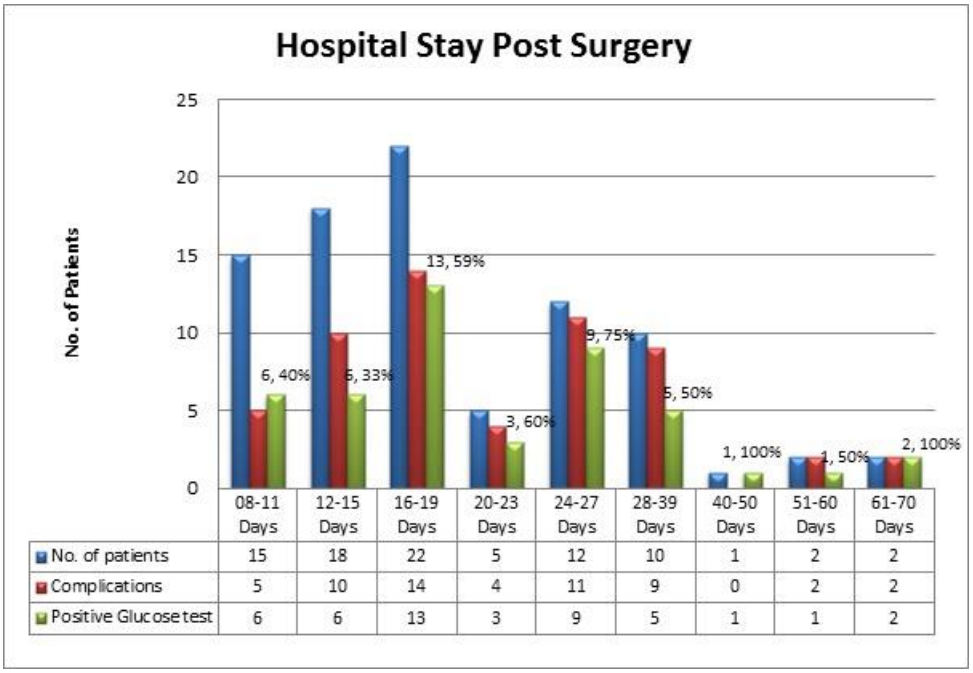

Figure 6-19 - Hospital stay post surgery

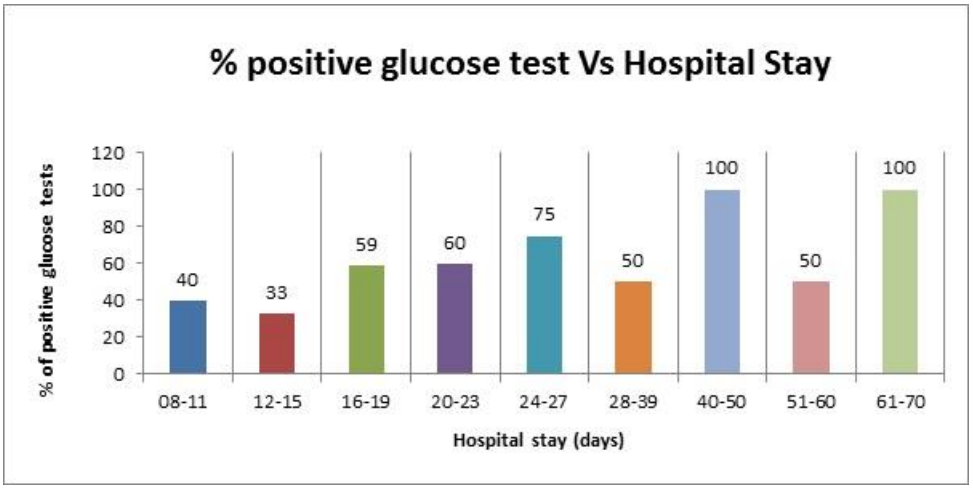

Figure 6-20 - % Positive Glucose Test

6.3.12 Diabetic patients and Small Intestinal Bacterial Overgrowth

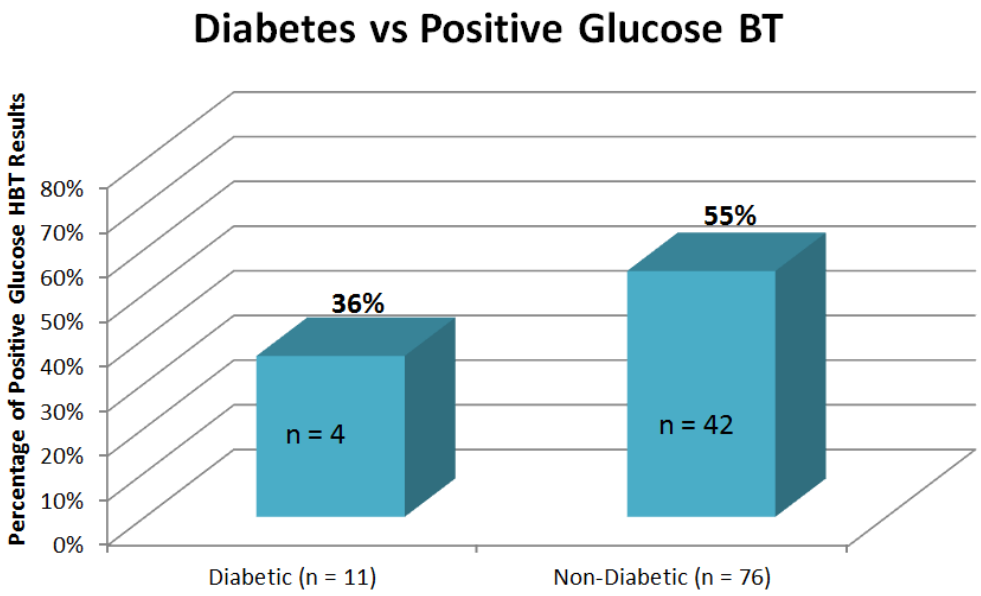

Figure 6-21 - Diabetic patients and SIBO

Patients without any documented diabetes (n=76; 87%) made up the majority of this patient cohort. These patients showed a 55% positive response for SIBO. Diabetic patients (n=11) had a 36% positive glucose result (refer to Figure 6-21). Therefore, even though diabetes is thought to be a contributing factor in the development of SIBO, it did not seem to be the case from the data shown above in this surgical group. The odds ratio for those patients with diabetes having a positive HBT versus those patients with no diabetes is OR = 0.46 (95% CI; 0.96, 2.80).

6.4 Incremental Time Sample Analysis of HBT results from patient cohort

Seven patients did not have a glucose breath test performed. This was because their fructose breath test was performed first and the patient did not want to return for further testing. Out of those patients that were only tested using fructose, 7 (100%) patients were positive for small intestinal bacterial overgrowth. The reason it was documented as being positive for SIBO as opposed to Fructose malabsorption was because of the early H2 rise in exhaled breath in all 7 patients. These positive tests showed a rise of >12ppm within 60 minutes in 5 patients and within 75 minutes in one patient (refer to Figure 6-22).

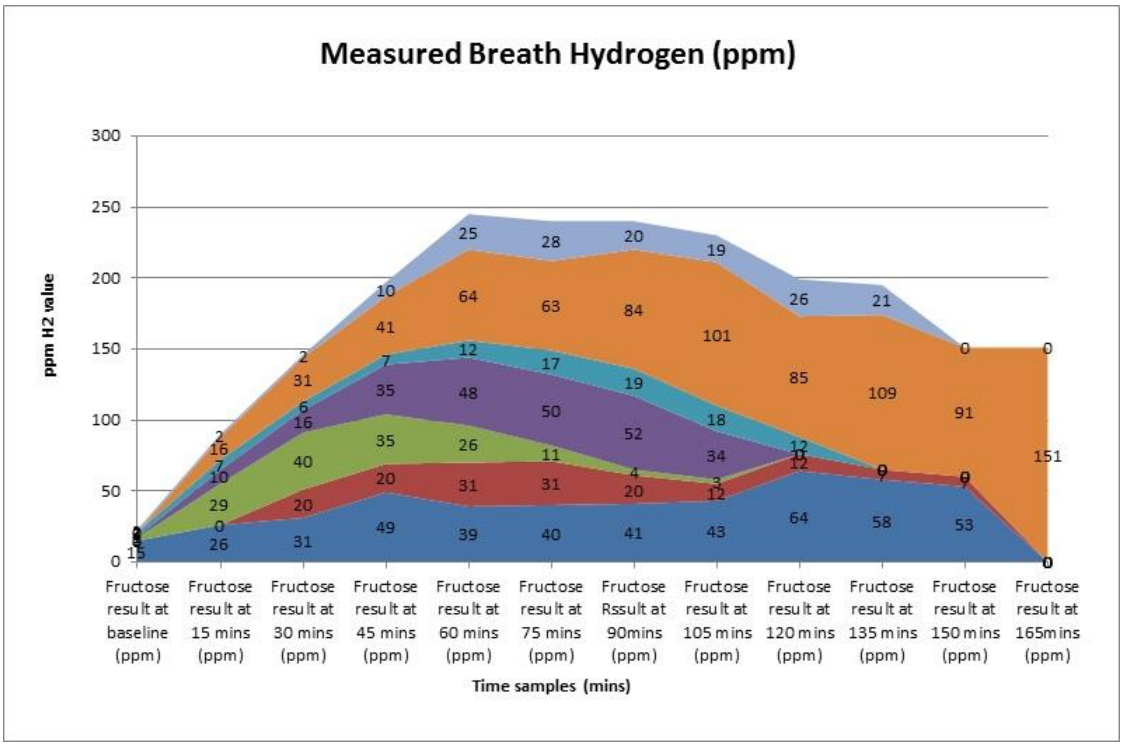

Figure 6-22 - Measured Breath Hydrogen (ppm)

A total of 87 patients had a glucose breath test performed. Table 6-8 lists the number of patients with positive and negative glucose HBT results. In total 46 patients (53%) tested positive for SIBO using the glucose HBT.

Table 6-8 - Glucose breath tests performed

Glucose BT	Total No. of Patients	% of Positive Glucose HBT's
Positive	46	53%
Negative	41	47%

Of those 87 patients that were tested for SIBO using glucose, the time frames at which point the patients were positive for SIBO is listed in Table 6-9 below. Those patients that had their HBT performed 7-12 months post-surgery, has the highest positive response for SIBO at 73%

Table 6-9 - Duration (months) that patients were tested for SIBO post surgery

Time post op (mths)	No. of studies	Positive	% of Positive Glucose HBT's
1-6 mths	55	25	45%
7-12 mths	22	16	73%
>1 year	10	5	50%

Table 6-10 below lists the 15 minute sampling increments and the corresponding positive glucose HBT result. Out of 46 patients positive for glucose breath tests, 96% had a positive rise within 75 minutes, 93% within 60 minutes, 85% within 45 minutes, 59% within 30mins and 24% within 15 minutes. The average time that patients were likely to show a positive result was 36.52 minutes.

Table 6-10 - Number of patients positive for glucose BT within specific time frame

Time (Minutes)	No. of Patients positive for glucose BT	% of Positive Glucose HBT's
15	11	24%
30	27	59%
45	39	85%
60	43	93%
75	44	96%
90	46	100%

6.5 Summary

Patient data was analysed in multiple categories ranging from body mass index and diagnosed malignancy, to their hospital stay and complications post-surgery. Table 6-11, Table 6-12 and Table 6-13 lists a summary of the findings discussed and displayed in chapter 8.

Table 6-11 - Summary of patient data and their Glucose BT result

Category	Details	Positive (n)	Negative (n)	Positive Glucose %
BMI	<18.5	1	0	100
	18.5-23	19	7	73
	25-30	9	10	47
	>30	11	13	46
Smoking Habit	Non-smoker	16	8	76
	Current Smoker	9	6	60
	Ex-smoker	20	28	42
Drinking Habit	Non-Drinker	10	3	77
	Social Drinker	29	26	53
	Ex-Drinker	2	4	33
	Heavy Drinker	3	7	30

Table 6-12 - Summary of patient data and their Glucose BT result

Category	Details	Positive (n)	Negative (n)	Positive Glucose %
Previous Malignancy	Previous malignancy	14	8	64
	No malignancy hx	32	32	50
Barrett's Histology	No Barrett's Oesophagus	21	22	49
	Barrett's Oesophagus	11	13	46
Tumour Morphology	Adenocarcinoma	41	35	54
	Squamous cell carcinoma	4	5	44
Surgery Type	Oesophagectomy	31	24	56
	Gastrectomy	15	17	47
Post-op complications	Complications	31	26	54
	No Complications	14	16	47
Diabetes	Non-Diabetic	42	34	55
	Diabetic	4	7	36

Table 6-13 - Summary of patient data and their Glucose BT result

Category	Details	Positive (n)	Negative (n)	Positive Glucose %
Radiotherapy	Radiotherapy	13	12	52
	No Radiotherapy	21	22	49
Chemotherapy	Chemotherapy	28	21	57
	No Chemotherapy	17	15	53
Hospital Stay (days)	08-11	6	9	40
	12-15	6	12	33
	16-19	13	9	59
	20-13	3	2	60
	24-27	9	3	75
	28-39	5	5	50
	40-50	1	0	100
	51-60	1	1	50
	61-70	2	0	100

Chapter 9

7 Discussion

A retrospective analysis of hydrogen breath testing (HBT) was performed over a three year period from 2008-2011 on all patients investigated in the GI Function unit. A total number of 194 patients who underwent 312 Hydrogen breath test procedures were reviewed. Results from this audit indicated a high positive rate for Small Intestinal Bacterial Overgrowth (SIBO) amongst those patients with a history of surgery for an oesophagectomy or gastrectomy. This 194 patient cohort was divided into two patients groups; those referred with IBS symptoms (n = 172), and those referred post major upper GI surgery (n = 22). Patients who had a HBT performed post oesophagectomy or gastrectomy had an 82% positive SIBO test result.

Based on these findings, a comprehensive analysis of hydrogen breath testing was carried out on a group of patients post oesophagectomy and gastrectomy. Exclusion criteria for this new research group included those patients that had complicated reconstructive surgery such as a colonic transposition, those patients that had their surgery for a non-malignant carcinoma such as a GIST or for Achalasia, and those patients that had their surgery prior to 2010. The timing between breath samples was reduced from the standard protocol of 20 minutes to 15 minutes to reflect the altered physiology of this patient group. A total of 106 patients were investigated for SIBO post oesophagectomy and gastrectomy. Of these, 99 patients were suitable for review in this research. Patients were investigated with both fructose and glucose substrate. Both of these substrates yielded similar results when testing for SIBO. The overall positivity for SIBO was 61% and 12 of these patients that were prescribed a course of Rifaximin 400 mg TDS returned to the GI unit for retesting and least one month after their antibiotic therpy was completed. Of these 12 patients that were retested post therapy, 42% were now negative for SIBO.

Following the results of this data, a third study group was initiated. A particular emphasis was placed on those patients (n=87) that had a glucose breath test performed. Results from these patients that had a glucose HBT performed was used for comprehensive analysis as the risk of false positive results was much lower than with fructose substrate. This is partly due to the potential post-surgical complication of dumping syndrome which could lead to a result of fructose malabsorption as opposed to SIBO. It can also be due to diminished fructose carriers resulting from intestinal inflammation. As part of a literature review conducted in this research, glucose substrate tends to be the standard practice in most GI units including the Royal Marsden Hospital in London, a specialist cancer centre.

Clinical and surgical data was scrutinised to try and establish a more efficient practice for HBT procedures. This group of patients are a challenging cohort who have had major reconstructive surgery of the GI tract, and have gone on to develop malabsorption and malnutrition difficulties. This has had a major impact on their quality of life post-surgery. The main focus of this study was to establish the incidence of SIBO in this patient group and develop a streamline protocol. There is no published data on this aspect of SIBO to date, so by creating a more patient friendly protocol, progress post-surgery can be managed more effectively though multi-disciplinary resources. Enhancement of such protocols was successfully demonstrated through the findings in this report and is now being implemented in the GI department.

A detailed review of this audit revealed that those patients who had a normal or low BMI were more positive for SIBO than those patients who were classified as being in the over-weight and obese categories. Similarly, those patients who were non-drinkers and non-smokers also had a higher positive glucose result compared to those patients who were current, ex or heavy smokers/drinkers, these trends did show a statistical significance. Lifestyle therefore did not seem to impact the overall glucose HBT result. Surprisingly there was a tendency for more normalisation of results with those patients who had poor lifestyle habits.

Diabetic patients had a notably lower positive result when compared to non-diabetic patients. This is consistent with the other lifestyle patterns and BMI discussed above. In contrast, those patients who had a history of previous malignancy and post-op complications showed a higher result for SIBO. This was also the case for patients who received multimodal therapy prior to their surgery but these findings are not statistically significant. Studies have shown that chemotherapy and radiotherapy can contribute to the development of SIBO. This was emphasised in this research and highlights the need for a prospective study on SIBO in patient's pre and post chemoradiotherapy. The length of hospital stay post-surgery reflects the SIBO results obtained. Overall, those patients who spent the least amount of time in hospital following surgery, i.e. a faster recovery period, were least likely to be positive for SIBO when compared to those patients who had a longer in-patient stay. Again, these trends did not show a statistical significance.

Overall, of the 87 patients who had a glucose HBT performed, 53% were positive for SIBO. When broken into time frames, 45% were positive when tested within 1-6 months of surgery. 73% were positive for SIBO when tested within 7-12 months of surgery and 50% were positive when tested for SIBO using glucose substrate after 1 year post surgery. As discussed in section 2.1, MMC's are an important contributing factor for small intestinal motility. It is thought that MMC disruption following surgery may take time to regulate and accommodate to the altered physiology. It may therefore be more beneficial to test patients for SIBO (unless very symptomatic) after approximately 12 months following surgery to allow for the MMC's to normalise and perhaps alter the small intestinal flora with its clearance function (Lawlor 2000).

Table 6-10 shows the 15 minute time segments and the corresponding positive percentage rate for SIBO. From the data shown, by the 45th minute marker, 85% of those patients with SIBO showed a positive result. This increased to 93% by the 60th minute. All patients that were positive for SIBO, showed a ppm rise of >12 by 90 minutes. The average time for patients to show a positive SIBO test was 36.52 minutes. Poor patient co-operation is one of the main disadvantages of the HBT due to time consumption, therefore

changing the timing protocol for the glucose HBT can be suggested. Currently, patients are informed that their glucose HBT can expect to take two hours with samples being taken at 15 minute intervals. From these findings, it was suggested that the HBT should take no longer than 90 minutes with the data trend indicating that the HBT will be terminated within 60 minutes if there is a rise of >12ppm. These changes have now been implemented in the GI Function Unit and have been captured by the local oesophageal cancer programme.

False positive breath tests can occur due to rapid intestinal transit (dumping syndrome). Therefore an early rise (within 60 minutes) is more likely to be due to SIBO than fermentation by colonic bacteria. This data can be used in conjunction with clinical symptoms and response to antibiotic therapy to aid diagnosis. Non-hydrogen producers may result in false negative results. This is thought to be in the region of 10%. The prevalence of SIBO post-surgery using glucose solution is comparable to the study by Paik *et al.* However, the overall positive result for SIBO using glucose was lower in our study (53% Vs 78%). This accountable difference may be due our inability to measure exhaled methane. In addition to this, the researchers used a different approach to their method of investigation. For example, they allowed their patients to smoke up to 30 minutes prior to their study which is known to increase hydrogen concentration levels in the blood. They also used a higher challenge dose of glucose (75g), took duplicate samples using different measurement devices and they had multiple exclusion criteria e.g. only gastrectomy patients with no evidence of disease recurrence for at least 6 months were included in study. We investigated patients from as early as 4 months following surgery. Both this study and my research showed similarities in the time segments for SIBO to be diagnosed. At 60 minutes post glucose ingestion, 100% of patients with positive HBT's showed a positive result, while we reported a 94% positive response for the same time segment. There is limited data and research done on SIBO in patients following an Oesophagectomy and Gastrectomy.

In patients with negative Hydrogen breath tests who are symptomatic with chronic diarrhoea, bile acid malabsorption (BAM) should be considered as a cause for their symptoms. This can be examined by performing a SeHCAT test. SeHCAT (tauroselcholic [75selenium] acid) is a radiopharmaceutical that is used for detecting bile acid malabsorption. It can also be performed to investigate ileal function, inflammatory bowel disease, chronic diarrhoea and enterohepatic circulation. There are several causes of chronic diarrhoea and sometimes a cause is unidentifiable following numerous investigations. Bile acid malabsorption is one cause of chronic diarrhoea. It is not life-threatening but can have a major impact on quality of life. It is currently the only test used to diagnose bile acid malabsorption (NICE 2012).

Recently, SeHCAT has become available to measure BAM as an investigation technique in this patient group in St. James's Hospital; however there is limited availability of this technique throughout the hospitals in the rest of Ireland. There are multiple reasons for this; one being that it is not yet recommended by NICE and another reason is because the SeHCAT needs to be conducted in a nuclear medicine unit and few hospitals are equipped with such departments. It is also quite expensive and a time consuming technique. If there is no known cause of the patient's chronic watery diarrhoea following other investigations, a trial therapy of bile acid sequestrants may be suggested.

In St. James's Hospital, patients are now being referred for SeHCAT if they are symptomatic with diarrhoea/steatorrhoea, where there has been no improvement or known cause of their symptoms following surgery. This investigation is being carried out in addition to Hydrogen breath testing in this patient group. A new malabsorption review chart has been devised by the Dietetic and surgical team for such patients to determine a cause of their diarrhoea/steatorrhoea (Appendix 5).

It must be remembered that SIBO can be the cause of bile acid malabsorption since the bacteria can deconjugate the bile acids affecting their re- absorption in the ileum. Therefore in patients with chronic watery diarrhoea who

demonstrate a positive HBT result post oesophagectomy and gastrectomy, antibiotic may be trialled before the bile acid sequestrants are prescribed. This is because the sequenstrants can have a side effect of constipation which could possibly give a false impression in their symptom improvement of chronic diarrhoea.

The use of HBT's and their role in the management of patients post major upper GI surgery looks promising. It is still an area that requires immense research and development. With the expanding knowledge and commitment of multi-disciplinary teams and surgical expertise, the future for patients with difficulties post-surgery is encouraging. The GI Function Unit in St. James's Hospital is determined to provide a specialist testing facility for these patients and will continue to promote and develop best practices for the future.

Chapter 10

8 Conclusion

Lifestyle factors including smoking and drinking habits as well as BMI had a statistically significant effect on the outcome of Hydrogen Breath Test (HBT) results. Those patients that had either a low BMI, were non-drinkers or non-smokers were more likely to have a positive glucose HBT.

Those patients who had a history of previous malignancy and post-operative complications showed a higher tendency towards a positive glucose HBT result, but this was not statistically significant.

In addition to the above statement, patients who had a longer post-operative hospital stay following their gastrectomy or oesophagectomy also tended to be positive for HBT using glucose substrate.

The percentage of patients positive for SIBO was greatest 6-12 months post-surgery. This may be attributed by the fact that intestinal motility including MMC's can take up to 12 months before it is resorted to its normal functioning state.

The positive patient cohort tested using glucose substrate demonstrated 93% positivity for SIBO at 60 minutes. The average time for patients to show a positive SIBO test was 36.52 minutes.

False positive results can occur because of dumping syndrome. Therefore a rise of >12ppm within 60 minutes is more likely to be from SIBO than colonic fermentation of the glucose substrate.

Although some patients (up to 10%) are non-hydrogen producers, those who are very symptomatic with negative HBT'S should be considered for bile acid malabsorption investigation using SeHCAT.

SeHCAT is now being used in St. James's hospital to investigate patients who are symptomatic with steatorrhoea/diarrhoea post-surgery. It is often overlooked as an investigation technique but can only be performed in a hospital with a nuclear medicine department.

SIBO can be the cause of BAM, therefore it should be considered to treat a positive HBT with antibiotic therapy and assess clinical response before treatment with prescribed bile acid sequestrants commences.

Recommendations:

- It is recommended that the testing protocol for glucose Hydrogen Breath Testing is reduced from 2 hours to 60 minutes for this group of patients if there is no rise in hydrogen levels.
- It is also recommended that symptomatic patients who have a negative Hydrogen Breath Test be referred for a SeHCAT test.
- Further studies are recommended in a prospective group of patients to identify SIBO pre and post treatment with both a Hydrogen and Methane monitor.

Glossary of Terms

Absorbent: In medical terms, are used to absorb water in the small intestine and colon. They are used to treat diarrhoea.

Achlorhydria: Refers to the reduction or absence of gastric acid secretions.

Adsorbent: (antidiarrheal) binds to caustic bacteria and eliminates them from the GI tract through their stool

Aerobic: (bacteria): utilize, grow and live in an oxygenated environment.

Aerophagia: the swallowing of air.

Anaerobic: (bacteria): Survive in the absence of oxygen.

Anticholinergic: a drug that blocks acetylcholine (neurotransmitter) in the brain. In the GI tract they are used to treat e.g. diarrhoea, muscular cramps/spasms

Arrhythmia: Irregular or abnormal heart rate or rhythm

Autonomic neuropathy: damage to the autonomic neurons. Symptoms vary depending on the nerves affected. In the GI tract, symptoms include diarrhoea, constipation, dysphagia, post-prandial nausea, early satiety etc.

Blind loops: can be formed as a result of surgery when part of the intestine is by-passed. Stagnant food and slow motility makes this area a high risk breeding ground for bacteria.

Casein: protein found in milk. Involved in the slow release of amino acids into the bloodstream

Chemotherapy: cancer treatment with the aim of destroying cancer cells. These drugs can be used to treat cancer anywhere in the body because they travel in the blood system.

Cirrhosis: occurs as a result of liver disease. Irreversible fibrous scar tissue replaces normal liver cells.

Colonocytes: colonic epithelial cells

Colony forming units: (CFU) is an estimate of the number of viable bacterial cells in a sample per Ml.

Co-morbidity: two or more diseases that occur simultaneously in a person with the initially diagnosed condition.

Cytokines: (small proteins) are released by cells and are involved in cell signalling. Their primary role is cell to cell communication in immune responses. They can affect the behaviour of the releasing cell or other cells.

Diverticula: an out-pouching or sac formed at a weak point in the wall of the gastrointestinal tract. Most commonly occurs in the colon

Enterocytes: epithelial cells of the small intestine

Fastidious anaerobes: organism that requires complex growth factors and amino acids. Can survive and grow with or without the presence of oxygen

Fistula: abnormal connection between two body structures e.g. between an artery and vein, between loops of the intestine etc.

Gastrectomy: a surgical procedure where part or all of the stomach is removed

Gastric atony: stomach wall is lacking in tone resulting in muscle weakness

Gastroparesis: paralysis of stomach wall resulting in poor or absent gastric motility.

Gram positive aerobes: retains the stain used in the gram's staining test. Can help determine what antibiotic to use, if there is infection present, or type of further tests required to determine cause of infection.

Hydrogen Breath Test: A technique used to measure the amount of hydrogen in parts per million (ppm) from a sample of exhaled air

Hyperosmolar: high osmolarity especially of a body fluid e.g. occurs in dehydration, hyperglycaemia

Hypomotility: decreased motility or movement

Ileocecal valve: a muscle valve that separates the distal part of the small intestine and the proximal part of the colon.

Immunoglobulin: an antibody used by the immune system. Produced by plasma cells and bind to specific antigens.

Interstitial Cystitis: a chronic and painful bladder condition.

Krebs cycle: part of cellular respiration providing energy that akes place within the mitochondria of a cell. A series of enzyme reaction with energy being released.

Lymphoid tissue: makes up the lymphatic system (e.g. white blood cells, bone marrow) involved in immune response. Include organs such as the spleen, thymus and lymph nodes.

Lysozyme: an enzyme (found in e.g. tears, salvia) that is capable of hydrolysing bacteria by destroying their cell walls.

Macrocytic anaemia: occurs when red blood cells are larger than normal and there is a reduction in the number of cells. Haemoglobin content is cell is often insufficient. This results in a reduction of oxygen reaching tissues and organs.

Mediators: a substance or a thing (e.g. enzyme or hormone) that is released from cells to carry out a process

Myenteric plexus: a nerve supply lying in the muscular wall of the oesophagus, stomach and intestine. Involved in the motility of the gastrointestinal tract.

Neo-adjuvant: administration of therapy before the primary treatment e.g. chemotherapy given before a surgical procedure.

Oesophagectomy: a surgical procedure where part or all of the oesophagus is removed

Osteomalacia: softening of the bones usually because of a lack of vitamin D.

Radiotherapy: a cancer treatment using high energy rays to control or kill cancer cells.

Saccharolytic: metabolism of carbohydrates for energy.

Short-chain fatty acids: produced in the colon as a result of fermentation. Butyric acid is an important short-chain fatty acid for proving energy to colonocytes and has anti-inflammatory/anti-carcinogenic properties.

SIBO: Small intestinal bacterial overgrowth. A condition where bacteria inhabit the small intestine in great quantities and can induce a variety of symptoms and other health conditions in an individual.

Tachycardia: a heart rate that is faster than the normal 60-100 bpm at rest.

Tetany: activation of nerve cells in the body that result in spasms or cramps of e.g. hands, feet, mouth. Usually due to low blood calcium or malfunctioning parathyroid gland.

Viscosity: (fluid) corresponds to the ‘thickness’ of a fluid. It is a measure of the fluids resistance to flow.

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Appendices

Appendix 1

Table A-1 - Patients tested for SIBO using Fructose and glucose solution

Patient No.	Age	M/F	Cancer patient	County	How long tested after surgery-mths	Surgery type	Positive SIBO	Positive Glucose	Positive/Fructose	On creony/n	Chmeo/radiation	Antibiotics
1	75	F	yes	Kilkenny	12	G	YES	YES	YES	NO	?	NO
2	80	M	Yes	Dublin	6	G	NO	NO	NO	NO	?	
3	48	M	Yes	Dublin	6	G	NO	NO	NO	YES	none	
4	58	F	Yes	Dublin	24	G	YES	YES	YES	YES	NONE	YES
5	64	M	Yes	Wicklow	10	O	YES	YES	YES	YES	BOTH	2 Courses
6	85	F	Yes	Dublin	7	G	YES	YES	NO	?	?	
7	50	M	Yes	Laois	15	O	YES	N/A	YES	YES	?	
8	70	F	Yes RIP	Tiperrary	6	O	YES	N/A	YES	YES	YES	RIP
9	60	M	Yes	Wexford	6	O	YES	YES	YES	YES	?	YES
10	53	F	Yes	Wexford	5	G &DO	YES	YES	YES	YES	NO	YES
11	70	M	Yes	Kildare	7	O	YES	N/A	YES	?	NO	
12	67	F	Yes	Kerry	9	O	YES	N/A	YES	?	?	
13	78	F	Ye	Dublin	18	O	YES	YES	YES	?	?	
14	53	M	Yes	Dublin	12+	G	NO	NO	NO	YES	CHEMO	
15	70	M	Yes	Dublin	24	O	NO	NO	NO	YES	?	
16	52	F	No	Leitrim	6	O	YES	YES	YES	YES	?	
17	70	F	Yes	Dublin	12+	O	YES	YES	YES	YES	NONE	YES x 2
18	79	M	Yes	Dublin	4	G	YES	N/A	YES	YES	NONE	
19	53	M	Yes	Dublin	12+	O	NO	NO	NO	TRIAL OFF	YES	
20	47	M	Yes	Waterford	6	O	YES	NO	YES	TRIAL OFF	CHEMO	
21	67	F	Yes	Wicklow	9	O	YES	N/A	YES	YES	NONE	

Patient No.	Age	M/F	Cancer patient	County	How long tested after surgery-mths	Surgery type	Positive SIBO	Positive Glucose	Positive/Fructose	On creony/n	Chmeo/radiation	Antibiotics
22	65	M	Yes	Dublin	4	O	YES	DNA	YES	YES	YES	YES
23	62	M	Yes	Wicklow	5	O	YES	YES	YES	YES	YES	YES
24	73	M	Yes	Galway	6	O	YES	NO	YES	YES	NO	YES
25	66	M	Yes	Donegal	9	O	YES	YES	YES	YES	NO	YES
26	54	F	Yes	Leitrim	12+	O	YES	YES	NO	NO	YES	YES
27	60	F	Yes	Louth	7	G	YES	YES	YES	YES	NO	YES
28	56	M	Yes	Dublin	7	O	YES	YES	YES	YES	CHEMO	YES
29	76	M	Yes	Dublin		G		NOT WANT	DON'T WANT	NO		
30	54	F	Tes	Limerick	15	O	NO	NO	NO	NO	YES	
31	59	M	Yes	Dublin	12	O	YES	YES	YES	YES	CHEMO	DISEASE RECURRENCE
32	72	M	Yes	Waterford	7	O	YES	YES	YES	NO	YES	NO
33	51	M	Yes	Wexford	7	O	YES	NO	YES	NO	NONE	
34	48	M	Yes	Galway	7	O & G &C	YES	NO	YES	NO	NONE	? DISEASE RECURRENCE
35	83	F	no	Offaly	15	G	YES	YES	NOT WANT	YES	?	
36	69	M	Yes	Clare	7	G	YES	YES	Yes	NO	CHEMO	NO
37	55	F	Yes	Longford	4	G	YES	YES	YES	YES	Chemo?	YES
38	69	M	Yes	Tipperary	12+	O	NO	NO	NO	?	YES	NO
39	74	M	Yes	Laois	7	G	YES	YES	NO	?	YES	YES
40	42	M	YES	Westmeath	6	O	YES	YES	NO	NO	Chemo	NO
41	62	M	YES	Dublin	20	O	No	No	No	?	Both	No
42	66	F	YES	Kildare	4	G	No	No	No	Yes	No	No
43	73	M	YES	Wexford	14	O	No	No	No	No	Both	No
44	71	M	YES	Waterford	12	O	No	No	No	Yes	Both	No
45	59	F	Yes	Tipperary	6	O	YES	YES	N/A	YES	NONE	? INPATIENT STUDY
46	72	M	Yes	Waterford	4	O	YES	YES	NO	?	BOTH	?

Patient No.	Age	M/F	Cancer patient	County	How long tested after surgery-mths	Surgery type	Positive SIBO	Positive Glucose	Positive/Fructose	On creony/n	Chmeo/radiation	Antibiotics
47	49	F	NO	Dublin	4	O	YES	YES	YES	?	NONE	?
48	65	male	yes	Westmeath	4	O	No	No	No	No	None	
49	76	Male	Yes	Dublin	4	G	No	No	No	No	Chemo	RIP
50	60	Male	Yes	Waterford	4	O	YES	Yes	Yes	Yes	none	Yes x 2
51	79	Male	Yes	Longford	5	O	No	No	No	No	none	
52	55	Male	Yes	Dublin	5	G	NO	NO	NO	?	Chemo	
53	58	Female	Yes	Dublin	4	O	YES	YES	NO	?	Both	no
54	72	Male	Yes	Longford	4	G	YES	NO	YES	?	Chemo (?&radio)	No; RIP
55	40	Female	Yes	Dublin	7	O	NO	NO	NO	Yes	Both	
56	64	Male	Yes	Tipperary	10	O and pg? and C	Yes	Yes	Yes	Yes	both	No
57	61	Female	Yes	Meath	4	O	Yes	Yes	Yes	?	none	
58	48	MALE	?	Kilkenny	24	G	No	No	No	?	?	
59	47	Female	Yes	Wexford	4	G	Yes	Yes	No	No	chemo	
60	79	Male	Yes	Wexford	9	G	Yes	Yes	n/a	?	Chemo	All time splenectomy
61	72	Female	Yes	Dublin	5	G	No	No	n/a	?	Chemo	Very poor technique
62	68	Female	Yes	Dublin	5	O	Yes	No	Yes	No	none	
63	72	Male	Yes	Dublin	5	O	NO	NO	n/a	?	?	
64	75	Male	Yes	Kerry	8	O	Yes	Yes	No	?	radio	
65	75	Male	Yes	Dublin	5	G	No	No	No	None	none	
66	67	Male	Yes	Galway	6	O	No	No	n/a	No	chemo	
67	72	Female	Yes	Dublin	5	G	Yes	Yes	n/a	No	chemo	
68	65	Male	Yes	Clare	5	O	No	No	n/a	No	both	RECURRENCE
69	53	Male	Yes	Westmeath	6	O	No	No	n/a	No	both	RECURRENCE
70	65	Male	Yes	Carlow	5	G	No	No	n/a	No	none	
71	75	Male	Yes	Galway	6	O	No	No	n/a	No	both	RIP

Patient No.	Age	M/F	Cancer patient	County	How long tested after surgery-mths	Surgery type	Positive SIBO	Positive Glucose	Positive/Fructose	On creony/n	Chmeo/radiation	Antibiotics
72	54	Male	Yes	Cavan	3	O	Yes	Yes	n/a	?	none	
73	72	Female	Yes	Waterford	5	G	Yes	Yes	n/a	No	none	
74	46	Male	Yes	Sligo	7	G	No	No	n/a	n/a	Both post op	
75	71	Male	Yes	Carlow	4	G	Yes	Yes	n/a	No	chemo	
76	67	Male	Yes	Kildare	5	G	No	No	n/a	No	none	
77	67	Male	Yes	Mayo	4	O	Yes	Yes	n/a	No	none	
78	80	Male	Yes	Monaghan	8	G	Yes	Yes	n/a	No	none	
79	61	Male	Yes	Sligo	7	O	No	No	n/a	No	none	
80	50	Female	Yes	Dublin	5	G	No	No	n/a	No	Chemo post-op	
81	60	Male	Yes	Dublin	5	O	Yes	Yes	n/a	No	Chemo pre & post	
82	70	Male	Yes	Monaghan	6	O	Yes	Yes	n/a	Yes	Chemo before	RIP
83	69	Male	Yes	Longford	27	O	Yes	Yes	n/a	No	none	
84	67	Female	Yes	Dublin	6	O	Yes	Yes	n/a	?	chemo	
85	58	Male	Yes	Dublin	6	O	No	No	n/a	?	none	
86	74	Female	Yes	Wexford	6	G	Yes	Yes	n/a	No	none	
87	51	Female	Yes	Dublin	5	O & G	Yes	Yes	n/a	Yes	chemo	Yes
88	76	Male	Yes	Offaly	5	G	No	No	n/a	No	none	
89	69	Male	Yes	Donegal	5	G	Yes	YES	n/a	No	Both pre & post	
90	73	Female	Yes	Tipperary	7	O	No	No	n/a	No	none	
91	74	Female	Yes	Wicklow	5	G & O	Yes	Yes	n/a	No	chemo	
92	64	Female	Yes	Laois	4	O	Yes	Yes	n/a	No	both	
93	59	Male	Yes	Dublin	6	G	No	No	n/a	No	Chemo	
94	35	Female	Yes	Offaly	5	G	Yes	Yes	n/a	Yes	chemo	Recurrence
95	48	Male	Yes	Limerick	5	G	No	No	n/a	No	chemo	
96	48	Male	No	Dublin	5	O	No	No	n/a	?	None	

Patient No.	Age	M/F	Cancer patient	County	How long tested after surgery-mths	Surgery type	Positive SIBO	Positive Glucose	Positive/Fructose	On creon y/n	Chmeo/radiation	Antibiotics
97	82	Male	Yes	Wexford	4	O	No	No	n/a	?	None	Rrecurrence
98	56	Female	Yes	Monaghan	4	G	No	No	n/a	?	chemo	
99	60	Female	Yes	Dublin	5	O	Yes	Yes	n/a	?	Both 2007	YES
100	68	Male	Yes	Westmeath	4	O	No	No	n/a	No	both	
101	51	Male	Yes	Sligo	5	O	No	No	n/a	No	Both pre and post	RECURRENCE
102	71	Male	Yes	Dublin	5	G	No	No	n/a	No	Chemo	
103	68	Male	Yes	Wicklow	5	O	No	No	n/a	No	both	A&e for dilo sever dysphagia * see notes
104	58	Male	Yes	Offaly	7	O	Yes	Yes	n/a	No	Chemo pre & post	NOT TREATED
105	75	Male	Yes	Wicklow	10	O	Yes	Yes	n/a	?	both	
106	57	Male	Yes	Wicklow	7	O	Yes	Yes	n/a	No	both	

Appendix 2

Table A-2 - Data collection from Surgical Patient Group

Patient No.	Age at Diagnosis	M/F	BMI at diagnosis	Symptoms at Diagnosis	Smoking status	Alcohol Status	Positive Glucose
1	72	F		Heartburn, epigastric pain, dyspepsia	Never smoked	Non drinker	YES
2	79	M		Dysphagia, Weight loss	Ex-Smoker	Social Drinker	NO
3	45	M	19.11	Anorexia,Epigastric pain,Lethargy,Epigastric discomfort,General malaise,Dyspepsia	Smoker	Heavy Drinker	NO
4	54	F		Vomiting,Anorexia,Weight loss,,Diarrhoea,Epigastric bloating/fullness,Early satiety	Never Smoked	Non Drinker	YES
5	61	M	24.62	Dysphagia	Not Documented	Not Documented	YES
6	83	F	19.59	Vomiting,Nausea,,Malaena,Constipation,Weight loss	Never Smoked	Social Drinker	YES
7	47	M	25.69	Heartburn,Epigastric pain,Odnyophagia,Dysphagia,Reflux,Other	Ex-Smoker	Social Drinker	N/A
8	67	F	18.01	Anorexia,Weight loss,Epigastric pain,Dysphagia Fatigue, Chest Pain, Anaemia	Never Smoked	Non Drinker	N/A
9	58	M	23.85	Reflux,Malaena	Never Smoked	Non-Drinker	YES
10	51	F	38.35	Other,Anaemia Flank pain	Never Smoked	Not Documented	YES
11	69	M	27.92	Reflux,Diarrhoea	Never Smoked	Social Drinker	N/A
12	76	F	16.77	Dysphagia,Reflux,Epigastric discomfort,Weight loss	Never Smoked	Social Drinker	N/A
13	73	F		Dysphagia,Anorexia,Weight loss	Never Smoked	Social Drinker	YES
15	67	M	31.25	Dysphagia,Hoarseness,Lethargy,Anaemia,General malaise	Ex Smoker	Social Drinker	NO
17	65	F	24.05	Epigastric pain,Regurgitation,Nausea,Reflux	Ex Smoker	Social Drinker	YES
18	78	M		Anaemia	Never Smoked	Heavy Drinker	N/A
19	48	M		Odnyophagia,Regurgitation,Dysphagia,Reflux	Ex Smoker	Social Drinker	NO
20	45	M	24.33	Weight loss,Dysphagia,Lethargy	Smoker	Social Drinker	NO

Patient No.	Age at Diagnosis	M/F	BMI at diagnosis	Symptoms at Diagnosis	Smoking status	Alcohol Status	Positive Glucose
21	65	F		None,Other picked up on routine barretts surveillance	Never Smoker	Social Drinker	N/A
22	63	M	21.05	Dysphagia,,Diarrhoea	Ex Smoker	Heavy Drinker	DNA
23	61	M	18.44	Weight loss,Lethargy,Epigastric discomfort,Epigastric bloating/fullness,Abdominal pain	Smoker	Social Drinker	YES
24	72	M	23.1	Weight loss,Dysphagia,Reflux,Epigastric discomfort,Dyspepsia	Ex Smoker	Social Drinker	NO
25	64	M	31.41	None	Ex Smoker	Heavy Drinker	YES
26	49	F	25.81	Dysphagia	Smoker	Social Drinker	YES
28	54	M	29.05	Weight loss,Epigastric pain,Dysphagia	Ex Smoker	Social Drinker	YES
30	52	F		Weight loss,Odnyophagia	Not documented	Not documented	NO
31	57	M	20.58	Dysphagia,Weight loss	Ex Smoker	Social Drinker	YES
32	71	M	30.4	Dysphagia	Ex Smoker	Social Drinker	YES
33	50	M		Haemetemesis,Nausea,Malaena,Weakness,Lethargy,Abdominal discomfort,Heartburn	Never Smoked	Social Drinker	NO
36	68	M	29.12	Weight loss,Dysphagia	Ex Smoker	Social drinker	YES
39	73	M	32.43	Weight loss,Dysphagia,Abdominal discomfort	Ex smoker	Non drinker	YES
40	41	M	20.87	Vomiting,Weight loss,Regurgitation,Dysphagia,Epigastric discomfort,Dyspepsia	Smoker	Non drinker	YES
41	59	M	35.38	Weight loss,Dysphagia,Lethargy,Epigastric discomfort,Abdominal discomfort	Never smoked	Heavy drinker	No
42	65	F		Lethargy,Anaemia	Ex smoker	Social drinker	No
43	71	M	26.5	Weight loss,Dysphagia,Weakness,Lethargy	Ex smoker	Social drinker	No
44	69	M	34.23	Reflux,Anaemia	Ex smoker	Social drinker	No
45	59	F	28.68	Weight loss,Dysphagia	Never smoked	Non drinker	YES
46	71	M	31.97	Odnyophagia,Dysphagia	Never smoked	Social drinker	YES
48	65	M	30.07	None	Ex	Social	No

Patient No.	Age at Diagnosis	M/F	BMI at diagnosis	Symptoms at Diagnosis	Smoking status	Alcohol Status	Positive Glucose
					smoker	drinker	
49	75	M	28.31	Reflux	Ex Smoker	Social Drinker	No
50	60	M	30.54	non specific chest pain	Ex smoker	Social Drinker	Yes
51	78	M	26.57	Weight loss,Dysphagia	Ex smoker	Social drinker	No
52	54	M	40.82	Heartburn,Epigastric pain,Dyspepsia	Ex smoker	Heavy drinker	NO
53	57	F	33.36	Weight loss,Dysphagia,Other Retrosternal pain, chest pain	Smoker	Social drinker	YES
54	71	M	30.07	Haemetemesis,Malaena,Collapsed,Anaemia Opportunistic finding of anaemia on investigation of shoulder injury	Ex smoker	Social drinker	NO
55	59	F	30.04	Dysphagia,Reflux,Dyspepsia	Ex smoker	Social drinker	NO
56	62	M	32.49	Odnyophagia,Hiccups,Dysphagia	Never smoked	Social drinker	Yes
57	60	F		Dysphagia	Ex smoker	Non drinker	Yes
59	46	F	21.09	Epigastric pain,Reflux,Abdominal discomfort	Smoker	Non drinker	Yes
60	78	M	22.43	Vomiting,Weight loss,Dysphagia	Ex smoker	Non drinker	Yes
61	71	F	33.24	Vomiting,Anorexia,Weight loss,Epigastric pain,Reflux,Diarrhoea,Lethargy,Waterbrash,Abdominal pain	Never smoked	Social drinker	No
62	68	F	25.64	Odnyophagia,Dysphagia,Epigastric discomfort,Abdominal discomfort	Ex smoker	Ex drinker	No
63	72	M	30.68	None	Ex smoker	Social drinker	NO
64	71	M	24.2	not documented	Ex smoker	Social drinker	Yes
65	73	M	31.67	Malaena,Anaemia	Ex smoker	Social drinker	No
66	65	M	38.05	Weight loss,Dysphagia	Ex smoker	Heavy drinker	No
67	71	F	21.08	Weight loss,Dysphagia	Never smoked	Social drinker	Yes
68	64	M	24.6	Weight loss,Dysphagia	Ex smoker	Heavy drinker	No
69	52	M	28.69	Heartburn,Epigastric pain,Regurgitation,Dyspepsia	Ex smoker	Social drinker	No

Patient No.	Age at Diagnosis	M/F	BMI at diagnosis	Symptoms at Diagnosis	Smoking status	Alcohol Status	Positive Glucose
70	64	M	35.54	Epigastric pain,Haemetemesis,Constipation,Flatulence,Shortness of breath,GI Bleed Haematemesis requiring 4 units of blood	Ex smoker	Social drinker	No
71	74	M	19.77	Weight loss,Dysphagia,Chest pain after eating	Ex smoker	Ex drinker	No
72	58	M	26.12	Epigastric pain,Dyspepsia	Ex smoker	Social drinker	Yes
73	68	F	24.34	Heartburn,Regurgitation,Reflux,Lethargy,Anaemia,General malaise,Shortness of breath	Never smoked	Social drinker	Yes
74	46	M		Vomiting,Anorexia,Weight loss,Nausea,Dysphagia,Abdominal discomfort Gastric outlet obstruction	Ex smoker	Social drinker	No
75	70	M	25.55	Dysphagia,Epigastric discomfort,Cough Back discomfort	Ex smoker	Social drinker	Yes
76	66	M		Anorexia,Weight loss,Early satiety,Abdominal pain Bloating, fullness	Smoker	Social drinker	No
77	66	M	28.06	Reflux	Smoker	Ex drinker	Yes
78	79	M	42.75	Epigastric discomfort	Never smoked	Social drinker	Yes
79	71	M		Heartburn ? Incidental pick up, presented to GP with subcutaneous lumps	Ex smoker	Social drinker	No
81	59	M	23.32	Weight loss,Dysphagia,Malaena,Anaemia,Abdominal discomfort	Never smoked	Social drinker	Yes
82	69	M	22.62	Weight loss,Odnyophagia,Dysphagia, Upper chest discomfort	Smoker	Heavy drinker	Yes
83	67	M		Dysphagia,,Malaena	Ex smoker	Social drinker	Yes
84	66	F	22.95	Heartburn,Dysphagia,Reflux	Smoker	Social drinker	Yes
85	56	M	31.62	Heartburn	Smoker	Heavy drinker	No
86	71	F	17.47	Anaemia	Ex smoker	Ex drinker	Yes
87	51	F	24.36	Weight loss,Regurgitation,Dysphagia,Early satiety	Ex smoker	Social drinker	Yes
88	75	M		Vomiting,Anorexia,Weight loss,Nausea,Epigastric discomfort	Ex smoker	Social drinker	No
89	68	M	27.06	Epigastric discomfort	Ex smoker	Ex drinker	YES
90	72	F		Reflux	Ex smoker	Non drinker	No
91	73	F	21.11	Vomiting,Weight loss,Dysphagia,,Anaemia,Abdominal pain Back pain	Never smoker	Social drinker	Yes

Patient No.	Age at Diagnosis	M/F	BMI at diagnosis	Symptoms at Diagnosis	Smoking status	Alcohol Status	Positive Glucose
92	63	F		Odnyophagia,Dysphagia,Epigastric discomfort	Never smoked	Social drinker	Yes
94	34	F	19.93	Weight loss,Nausea,Dysphagia,,Early satiety Hair loss. pulsating lump in abdomen	Never smoked	Social drinker	Yes
95	47	M	24.89	Weight loss,Epigastric pain,Belching,Odnyophagia,Dysphagia,Reflux	Never smoked	Social drinker	No
96	44	M	38.27	Heartburn,Epigastric pain,,Lethargy,Anaemia,General malaise Night sweats	Ex smoker	Social drinker	No
97	82	M	26.82	Weight loss,Dysphagia	Ex smoker	Non drinker	No
98	55	F		Dyspepsia,Abdominal pain	Never smoked	Non drinker	No
99	59	F	21.71	Dysphagia,Reflux,Dyspepsia	Ex smoker	Social drinker	Yes
100	67	M	25.61	Weight loss,Hiccups,Dysphagia,Lethargy	Ex smoker	Social drinker	No
101	50	M	26.59	Vomiting,Weight loss,Epigastric pain,Dysphagia	Smoker	Heavy drinker	No
102	70	M	29.76	Weight loss,Dysphagia,Reflux,Anaemia,Abdominal discomfort	Never smoked	Social drinker	No
103	67	M	24.98	Weight loss,Odnyophagia,Haemetemesis,Dysphagia,Anaemia Hb 7.5, received 2 units blood	Smoker	Ex drinker	No
104	57	M	25.1	Weight loss,Hiccups,Regurgitation,Dysphagia	Smoker	Heavy drinker	Yes
105	74	M	25.14	Weight loss,Regurgitation,Dysphagia	Ex smoker	Non drinker	Yes
106	56	M	33.17	Weight loss,Odnyophagia,Dysphagia,,Dyspepsia Retrosternal pain	Ex smoker	Social drinker	Yes

Appendix 3

ST. JAMES'S HOSPITAL
DUBLIN . IRELAND

Test Type
Glucose

Health Care Professional
GI Function Unit
St James Hospital
Dublin
Tel: 01 4162888
D8 Fax: 01 4103468

Patient Details
Example Post Upper GI Surgery ID: 123456
St. James's Hospital Male
Dublin 8 20/02/1952
Ireland

Challenge Dose
Dosage: 50g
Substance: Glucose Solution

Interpretation
Negative Glucose study
Post Oesophagectomy 6/12

Date	PPM
25/08/2014 12:20:00	2
25/08/2014 12:35:00	2
25/08/2014 12:50:00	3
25/08/2014 13:05:00	2
25/08/2014 13:20:00	5
25/08/2014 13:35:00	3
25/08/2014 13:50:00	3
25/08/2014 14:05:00	2
25/08/2014 14:20:00	2

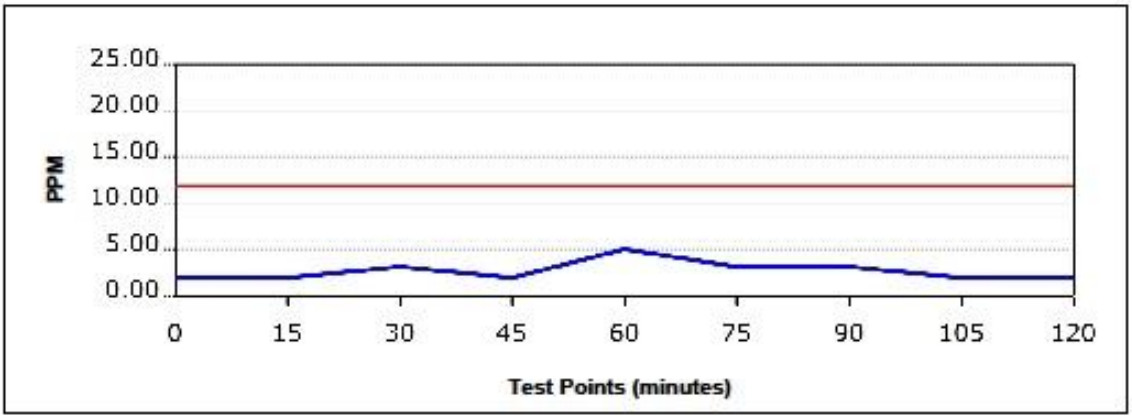

Figure A-1 - Example of a Negative Glucose HBT post surgery

ST. JAMES'S HOSPITAL
DUBLIN . IRELAND

Test Type

Glucose

Health Care Professional

GI Function Unit
St James Hospital
Dublin

Tel: 01 4162888
D8 Fax: 01 4103468

Patient Details

Example Post Upper GI Surgery ID: 123456
St. James's Hospital Male
Dublin 8 20/02/1952

Ireland

Challenge Dose

Dosage: 50g

Substance: Glucose Solution

Interpretation

Positive Glucose study for SIBO
Post Oesophagectomy x 6/12

Date	PPM
25/08/2014 12:06:00	5
25/08/2014 12:20:00	13
25/08/2014 12:35:00	15
25/08/2014 12:50:00	26
25/08/2014 13:05:00	32
25/08/2014 13:20:00	30
25/08/2014 13:35:00	28
25/08/2014 13:50:00	18
25/08/2014 14:05:00	9

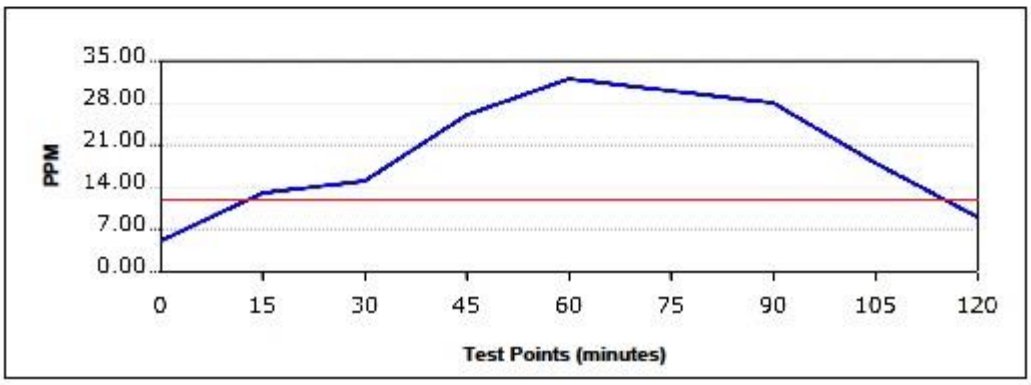

Figure A-2 - Example of a Positive Glucose HBT post surgery

Appendix 4

Specification

Concentration range:	0-500ppm hydrogen (H_2)
Display:	Colour LCD with 1ppm increments
Detection principle:	Electrochemical sensor
Accuracy (repeatability of reading):	±10%
Carbon monoxide cross-sensitivity:	<1%
Batteries:	3 x AA (LR6 or equivalent) alkaline batteries 1 x CR2032 Lithium coil cell (3v)
Response time:	Typically <45 seconds
Operating temperature range:	15-35°C (storage 0-50°C)
Operating humidity:	10-90% (storage 0-95%) non-condensing
Sensor operating life:	2-3 years, 12 month warranty
Sensor sensitivity:	1ppm
Transport/Storage Humidity:	15%-90% rh non condensing
Dimensions:	Approx. 44 x 77 x 138 mm
Weight:	Approx. 250g including batteries
Construction:	Case: Polycarbonate/ABS blend with elastomeric overmould. D-piece: Polypropylene

Figure A-3 - Gastro+ Operating manual Specification Sheet

Symbols

Direct Current

Degree of protection against electric shock: Type BF applied part

Type of protection against electric shock: Internally Powered Equipment

Please refer to the warnings and safety notes in the manual

Consult instructions for use

Degree of protection against ingress of liquid: IPXO - not protected against water ingress

Degree of safety application in the presence of a flammable anaeshetic mixture with air, oxygen or nitrous oxide: Equipment not suitable for use in the presence of flammable mixtures.

Environment
The Gastro+ complies with the directive EN60601-1-2 electromagnetic compatability but can be affected by cellular phones and by electromagnetic interference exceedding the levels specified in EN50082:1. This equipment should be moved if necessary to avoid interference.

Figure A-4 - Gastro+ Operating manual Specification Sheet

Appendix 5

NATIONAL OESOPHAGEAL AND GASTRIC CANCER C
Oesophageal and Gastric Clinic

A Guide to Investigate Symptoms of Malabsorption post Oesophagectomy or Gastrectomy

Symptoms of malabsorption can include:

- Steatorrhoea (stools that are pale / foul-smelling / oily / floating / difficult to flush / bulky)
- Diarrhoea
- Bloating
- Excessive wind (oral or rectal)
- Weight loss

1. If malabsorption is suspected, ask the patient to complete the *Malabsorption Symptom Questionnaire* to accurately identify and record symptoms.
2. Patients can have more than one cause for their symptoms and a series of investigations may be required to elucidate the cause or causes.
3. Ideally all investigations are ordered at the same time and the patient reviewed back in clinic with all the results.
4. Advise patients that it may take up to 4 hospital visits and a 6-8 week time frame to have all results available.

Investigation	Rationale	Practical Considerations
Malabsorption Symptom Questionnaire	To accurately identify and record symptoms.	Quick self-completion questionnaire. Find in clinic folder and on completion file under "Functional Investigations" in the medical notes. Should be repeated pre and post intervention to assess / measure symptom change.
Faecal Elastase	Exocrine pancreatic insufficiency (EPI)	Advise patient on returning a stool sample to GEMS OPD nurses or the Central Pathology Lab on their next hospital visit. Formed sample required. Takes 2-3 weeks to be reported.
Glucose Hydrogen Breath Test	Small intestinal bacterial overgrowth (SIBO)	Complete Upper GI Function Lab referral form by hand. Drop form in to the GI Function Lab after clinic.
SeHCAT scan	Bile acid malabsorption (BAM)	Order Nuclear Medicine Isotope SeHCAT Scan on EPR. Requires 2 visits to Nuclear Medicine to complete
Blood Screen Urea and electrolytes FBC Glucose Liver Function Tests Thyroid Function Tests CRP tTG & Ig A Ferritin, Red Cell Folate & B12 Vitamin A, D & E	Routine Bloods Coeliac Disease Micronutrient Deficiencies	Direct to phlebotomy for bloods. Fat soluble vitamins A, D & E take about 3 weeks to be reported.
Referral to Clinical Nutrition for Nutritional Assessment	Assessment of dietary adequacy Education on pancreatic enzymes Treatment of micronutrient deficiencies Modification of fat or fibre or lactose intake	Order clinical nutrition outpatient referral on EPR. Highlight suspected malabsorption post oesophagectomy or gastrectomy. Appointment will be scheduled when all of the investigations are completed and results available.

Figure A-5 - Malabsorption form for post Oesophagectomy and Gastrectomy Patients

Appendix 6

GASTRECTOMY/OESOPHAGECTOMY QUESTIONAIRE GI Function Unit

MRN _____

NAME_____

DOB _____

HEIGHT_____ WEIGHT_____ BMI_____

(PRE AND POST SURGERY)

DATE OF SURGERY

TYPE OF SURGERY

CHEMO/RADIATION

REASON FOR SURGERY

SYMPTOMS

ONSET OF SYMPTOMS POST SURGERY

SEVERITY OF SYMPTOMS

ANY OTHER MEDICAL HX

PRESCRIPTION MEDICATION

Appendix 7

Publications and Presentations

- Poster Presentation, Irish Society for Clinical Nutrition & Metabolism 2nd Scientific Conference, Clyde Court Hotel, 5th and 6th March 2013 ‘Prevalence of Small Intestinal Bacterial Overgrowth Post Oesophagectomy’

- Poster presentations, Irish Society of Gastroenterology 50th Anniversary, 23rd November 2012. ‘Prevalence of Small Intestinal Bacterial Overgrowth Post Oesophagectomy’

- Presentation ‘Hydrogen Breath Testing’ GI Physiology Day, Conference centre, Stewarts Hospital, Palmerstown, Friday 7th October 2011

- Irish Society of Gastroenterology Spring meeting, Hotel Kilkenny, 29th-30th April 2010. Poster presentation ‘Hydrogen Breath Testing. A two-year audit’.

- Currently (2016) preparing a paper and abstract submission to the British Society of Gastroenterology, AGM, June 2016