

World Journal of *Gastrointestinal Surgery*

World J Gastrointest Surg 2021 July 27; 13(7): 620-733



Contents

Monthly Volume 13 Number 7 July 27, 2021

OPINION REVIEW

- 620** Endoscopic ultrasound guided gastrojejunostomy for gastric outlet obstruction
Stefanovic S, Draganov PV, Yang D

MINIREVIEWS

- 633** Current status of treatments of pancreatic and peripancreatic collections of acute pancreatitis
Xiao NJ, Cui TT, Liu F, Li W
- 645** Closure techniques in exposed endoscopic full-thickness resection: Overview and future perspectives in the endoscopic suturing era
Granata A, Martino A, Ligresti D, Zito FP, Amata M, Lombardi G, Traina M
- 655** Management of early rectal cancer; current surgical options and future direction
Chavda V, Siaw O, Chaudhri S, Runau F
- 668** Robotic donor hepatectomy: Are we there yet?
Rammohan A, Rela M
- 678** Gastrectomy impact on the gut microbiome in patients with gastric cancer: A comprehensive review
Maksimaityte V, Bausys A, Kryzauskas M, Luksta M, Stundiene I, Bickaite K, Bausys B, Poskus T, Bausys R, Strupas K

ORIGINAL ARTICLE

Retrospective Study

- 689** Novel parameter based on lipid indicators ratio improves prognostic value of plasma lipid levels in resectable colorectal cancer patients
Gu JN, Yao S, Cao YH, Deng SH, Mao FW, Jiang HY, He YT, Li XY, Ke SQ, Li HL, Li H, Liu XH, Liu HL, Wang JL, Wu K, Liu L, Cai KL

SYSTEMATIC REVIEWS

- 702** Acute mesenteric ischemia and small bowel imaging findings in COVID-19: A comprehensive review of the literature
Pirola L, Palermo A, Mulinacci G, Ratti L, Fichera M, Invernizzi P, Viganò C, Massironi S

META-ANALYSIS

- 717** Efficacy and safety of early oral feeding in postoperative patients with upper gastrointestinal tumor: A systematic review and meta-analysis
Hao T, Liu Q, Lv X, Qiu J, Zhang HR, Jiang HP

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Kun-Ming Chan, MD, Professor, Department of General Surgery and Chang Gung Transplantation Institute, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, Taoyun 33305, Taiwan. chankunming@cgmh.org.tw

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (WJGS, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, etc.

INDEXING/ABSTRACTING

The WJGS is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for WJGS as 2.582; IF without journal self cites: 2.564; 5-year IF: 3.378; Journal Citation Indicator: 0.53; Ranking: 97 among 212 journals in surgery; Quartile category: Q2; Ranking: 73 among 92 journals in gastroenterology and hepatology; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Jia-Hui Li; **Production Department Director:** Xiang Li; **Editorial Office Director:** Ya-Juan Ma.

NAME OF JOURNAL

World Journal of Gastrointestinal Surgery

ISSN

ISSN 1948-9366 (online)

LAUNCH DATE

November 30, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Shu-You Peng, Varut Lohsiriwat, Jin Gu

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-9366/editorialboard.htm>

PUBLICATION DATE

July 27, 2021

COPYRIGHT

© 2021 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/gerinfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/gerinfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Gastrectomy impact on the gut microbiome in patients with gastric cancer: A comprehensive review

Vaidota Maksimaityte, Augustinas Bausys, Marius Kryzauskas, Martynas Luksta, Ieva Stundiene, Klaudija Bickaite, Bernardas Bausys, Tomas Poskus, Rimantas Bausys, Kestutis Strupas

ORCID number:

Vaidota Maksimaityte 0000-0002-9307-0037; Augustinas Bausys 0000-0003-1848-2960; Marius Kryzauskas 0000-0002-6373-9721; Martynas Luksta 0000-0001-8023-9908; Ieva Stundiene 0000-0002-2569-3638; Klaudija Bickaite 0000-0003-3952-3223; Bernardas Bausys 0000-0002-6542-4045; Tomas Poskus 0000-0002-6931-6041; Rimantas Bausys 0000-0003-4718-6810; Kestutis Strupas 0000-0002-1690-937X.

Author contributions:

Maksimaityte V and Bausys A contributed equally to this work; Bausys R and Strupas K conceptualized and designed the work; Maksimaityte V, Bausys A, Kryzauskas M, Luksta M, Stundiene I, Bickaite K, Bausys B, and Poskus T performed the literature review and critical revision of the studies; Bausys A and Maksimaityte V prepared the manuscript; Kryzauskas M, Luksta M, Stundiene I, Bickaite K, Bausys B, Poskus T, Bausys R, and Strupas K revised the manuscript; all authors read and approved the final version of the manuscript.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Open-Access: This article is an open-access article that was

Vaidota Maksimaityte, Augustinas Bausys, Marius Kryzauskas, Martynas Luksta, Ieva Stundiene, Tomas Poskus, Rimantas Bausys, Kestutis Strupas, Clinic of Gastroenterology, Nephrourology, and Surgery, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius 03101, Lithuania

Augustinas Bausys, Rimantas Bausys, Department of Abdominal Surgery and Oncology, National Cancer Institute, Vilnius 08660, Lithuania

Klaudija Bickaite, Bernardas Bausys, Faculty of Medicine, Vilnius University, Vilnius 03101, Lithuania

Corresponding author: Augustinas Bausys, MD, Doctor, Clinic of Gastroenterology, Nephrourology, and Surgery, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Ciurlionio str. 21, Vilnius 03101, Lithuania. abpelikanas@gmail.com

Abstract

Gastric cancer is one of the most common malignancies worldwide and gastrectomy remains the only potentially curative treatment option for this disease. However, the surgery leads to significant physiological and anatomical changes in the gastrointestinal (GI) tract including loss of the gastric barrier, an increase in oxygenation levels in the distal gut, and biliary diversion after gastrectomy. These changes in the GI tract influence the composition of the gut microbiome and thus, host health. Gastrectomy-induced dysbiosis is characterized by increased abundance of typical oral cavity bacteria, an increase in aero-tolerant bacteria (aerobes/facultative anaerobes), and increased abundance of bile acid-transforming bacteria. Furthermore, this dysbiosis is linked to intestinal inflammation, small intestinal bacterial overgrowth, various GI symptoms, and an increased risk of colorectal cancer.

Key Words: Gut microbiota; Dysbiosis; Gastric cancer; Gastrectomy; Microbiome; Comprehensive review

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Lithuania

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 13, 2021

Peer-review started: March 13, 2021

First decision: April 6, 2021

Revised: April 19, 2021

Accepted: May 25, 2021

Article in press: May 25, 2021

Published online: July 27, 2021

P-Reviewer: Chen F, Liang Y, Socca B

S-Editor: Fan JR

L-Editor: Webster JR

P-Editor: Wang LL



Core Tip: In most cases of gastric cancer (GC) the only life-saving treatment is gastrectomy. Gastrectomy results in significant changes in gut microbiota: Higher abundance of oral cavity bacteria, aero-tolerant bacteria, and bile transforming bacteria, and these changes in the microbiome are related to host health. In this review we discuss current knowledge and the results of recent studies on the changes in gut microbiome after gastrectomy in patients with a history of GC.

Citation: Maksimaityte V, Bausys A, Kryzauskas M, Luksta M, Stundiene I, Bickaite K, Bausys B, Poskus T, Bausys R, Strupas K. Gastrectomy impact on the gut microbiome in patients with gastric cancer: A comprehensive review. *World J Gastrointest Surg* 2021; 13(7): 678-688

URL: <https://www.wjgnet.com/1948-9366/full/v13/i7/678.htm>

DOI: <https://dx.doi.org/10.4240/wjgs.v13.i7.678>

INTRODUCTION

Gastric cancer (GC) is an important oncological problem responsible for over 1000000 new cases and more than 783000 deaths worldwide annually, making it the fifth most common cancer and the third leading cause of cancer death[1]. Surgery remains the only potentially curative treatment option for this disease[2]. However, gastrectomy has some adverse effects in long-term survivors, including persistent gastrointestinal (GI) symptoms[3-5] and an increased risk of metachronous cancers[6-8]. Gastrectomy leads to significant changes in the GI tract, including changes in pH, oxygenation levels, and biliary diversion. These alterations of the GI tract create a strong impetus on changes in the gut microbiome (Figure 1), which was suggested to be involved in postoperative outcomes[6]. Gastrectomy-induced dysbiosis is characterized by increased abundance of typical oral cavity bacteria, an increase in aero-tolerant bacteria (aerobes/facultative anaerobes), and increased abundance of bile acid-transforming bacteria.

The microbiome of the human gut is a complex and diverse population of bacteria, fungi, archaea, and viruses that inhabit the intestinal tract, mainly the large intestine[9, 10]. The stable human gut bacterial species are divided into six main phyla: *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, *Proteobacteria*, *Verrucomicrobia*, and *Euryarchaeota* [11]. These microbes have tremendous potential to impact host physiology, both in health and disease[12]. They contribute metabolic functions, protect against pathogens, educate the immune system, and, through these basic functions, affect directly or indirectly most of our physiologic functions[12]. Recent advancements revealed the gut microbiome's role in a series of different diseases including Alzheimer's disease [13,14], obesity[15], inflammatory bowel diseases (IBD)[16,17], cancer[18,19], functional GI disorders[20], and others. Furthermore, the role of the microbiome in postoperative weight loss and other outcomes are documented after sleeve gastrectomy and Roux-en-Y gastric bypass in bariatric patients[21-26]. Several recent studies investigated the gut microbiome after gastrectomy for GC[6,27-29]. This comprehensive review provides an overview of the current evidence on gut microbiome after gastrectomy for GC and its clinical implication.

LITERATURE SEARCH

A comprehensive literature search was conducted using the PubMed database up to 31st December, 2020. The search terms used were "gastrectomy AND microbiome". No time restrictions for publications were used, but only manuscripts published in the English language were reviewed. All titles and abstracts were independently reviewed by two reviewers (V.M. and A.B.) to identify clinical studies investigating the impact of gastrectomy on the gut microbiome in GC patients. After relevant abstracts were identified the full-text articles were retrieved. To ensure a comprehensive literature search an additional manual search of the reference lists was performed.

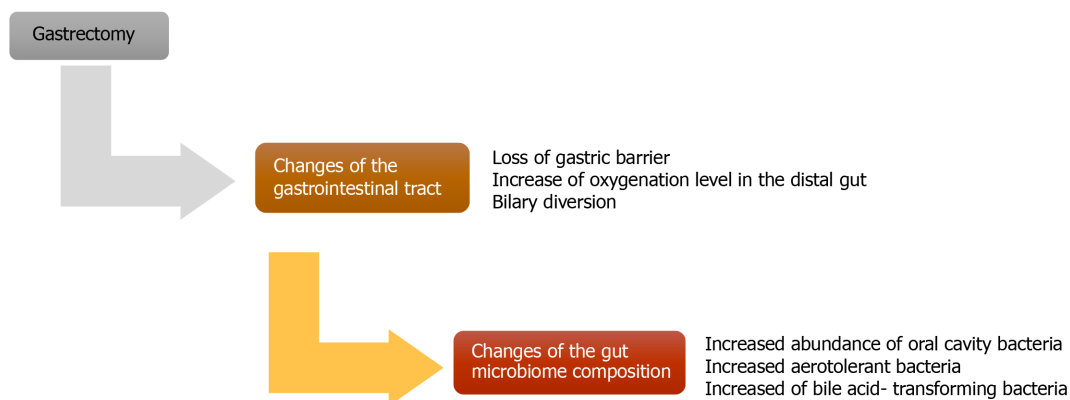


Figure 1 Gastrectomy impact on the gastrointestinal tract environment and gut microbiome.

COMPREHENSIVE REVIEW

Following a comprehensive review of the current literature, we identified 4 studies which investigated the gut microbiome after total or subtotal gastrectomy for GC, and these are summarized in Table 1. Three of these four studies were cross-sectional and investigated gut microbiome composition in GC patients at a median time of 3.75 years [27], 5 years [6], and 8.25 years [28] after gastrectomy and compared it with the corresponding controls. One small-scale study was longitudinal and investigated the gut microbiome composition before and approximately one week after gastrectomy [29].

Gut microbiome diversity and richness may be related to host health [30]. A reduction in the GI microbiome biodiversity was reported in obesity, inflammatory bowel disease, colorectal malignancy, and type 2 diabetes [21,30-33]. The impact of gastrectomy on bacterial richness and alpha diversity remains controversial because of conflicting results in current studies. Erawijantari *et al* [6] showed increased richness and diversity by increased Chao1 and Shannon indices in gastrectomized patients [6]. However, bacterial richness and alpha diversity may depend on the type of GI tract reconstruction. The study by Lin *et al* [28] showed increased richness and alpha diversity only after subtotal gastrectomy with Roux-en-Y reconstruction (RYGJ), but not in the case of Billroth II reconstruction (B2) [28]. Furthermore, similar richness and even decreased alpha diversity after subtotal gastrectomy with B2 reconstruction was reported by Horvath *et al* [27]. The impact of gastrectomy on bacterial richness and alpha diversity seems to be a long-term effect of the surgery since these changes were not observed by Liang *et al* [29] in the early perioperative period [29]. All the studies managed to identify and highlight specific features of the gut microbiome composition in the postsurgical period [27-29,34].

GASTRIC BARRIER LOSS AFTER GASTRECTOMY AND ITS IMPACT ON GUT MICROBIOME COMPOSITION

One of the typical changes in the GI tract after subtotal gastrectomy includes loss of the gastric barrier [27] due to reduced gastric acid secretion [27,35-37]. A pH of 4 is considered a threshold value for a powerful bactericidal effect [38] and it is significantly exceeded after subtotal gastrectomy, as the gastric pH increases from physiological levels to values above 6.0, irrespective of the type of reconstruction [39]. A very similar increase in gastric pH from approximately 2.0 to over 6.0 is described following proton pump inhibitor (PPI) intake [27]. In such conditions oral bacteria may survive during gastric passage and colonize the distal part of the GI tract, causing gut microbiome oralization, the phenomenon previously described in PPI users [40-43]. The comparable loss of gastric barrier function after subtotal gastrectomy and by PPI use may result in a similar impact on the gut microbiome.

Thus, it was not surprising, that a higher abundance of typical oral cavity bacteria-*Streptococcus*, *Veillonella*, *Prevotella*, *Oribacterium*, and *Mogibacterium* [44], were observed in the gut microbiome of gastrectomized patients [6,27,28]. Some of these bacteria are linked to host health and treatment efficacy. A recent study linked *Veillonella* with tumor response to Nivolumab in patients with progressive GC [45]. *Streptococcus* is a prevalent bacterial taxon in the oral cavity and the most commonly described

Table 1 Clinical studies investigating gut microbiome composition in patients after gastrectomy for gastric cancer

Ref.	Type of study	Participants (groups)	Exclusion criteria	Type of gastrectomy and method of reconstruction	Main findings of the study	Other metabolites investigated
Erawijantari <i>et al</i> [6], 2020	CSS	Gastrectomy group: Patients with a history of gastrectomy for GC ($n = 50$). Control group: Healthy controls without a history of gastrointestinal surgery ($n = 56$)	Recurrence of gastric cancer (gastrectomy group). History of gastrointestinal surgery (for controls)	Total ($n = 12$) gastrectomy and subtotal gastrectomy ($n = 38$). Types of reconstruction: Stomach-stomach ($n = 1$); Billroth I ($n = 2$); Jejunal interposition ($n = 6$); Pylorus-preserving gastrectomy ($n = 8$); Roux-en-Y ($n = 29$)	Higher species diversity and richness in gastrectomized patients. Higher abundance of aerobes, facultative anaerobes, and oral microbes in gastrectomized patients	Phosphate and amino acid transporters were more abundant in gastrectomized patients. Primary and conjugated forms of bile acid enriched in the control group and deoxycholic acid more abundant in gastrectomized patients
Liang <i>et al</i> [29], 2019	LS	Gastrectomy group: Patients with a diagnosed GC one week before ($n = 20$) and ≥ 7 d after ($n = 6$) gastrectomy. Control group: Healthy controls ($n = 22$)	History of antibiotics, PPI or H2 receptor antagonist use 1 mo prior to inclusion. Endoscopic finding of peptic ulcer, tumor rupture, pyloric obstruction. Patients with a history of radiotherapy/chemotherapy and/or previous surgery	Distal gastrectomy ($n = 6$). Types of reconstruction: Billroth II ($n = 1$); Roux-en-Y ($n = 5$)	Increased abundance of <i>Bacteroidetes</i> , <i>Fusobacteria</i> , and <i>Verrucomicrobia</i> and decreased abundance of <i>Proteobacteria</i> , <i>Firmicutes</i> , and <i>Actinobacteria</i> after distal gastrectomy. The richness and diversity by Chao1; ACE; Shannon; and Simpson indices were similar before and after distal gastrectomy. LEfSe analysis attributed <i>Verrucomicrobiae</i> (genus <i>Akkermansia</i>) and genus <i>Escherichia/Shigella</i> , <i>Lactobacillus</i> , and <i>Dialister</i> to patients after gastrectomy, and the genus <i>Klebsiella</i> to patients before gastrectomy	Significantly decreased level of valeric acid after distal gastrectomy
Horvath <i>et al</i> [27], 2021	CSS	Gastrectomy group: Patients with a history of distal gastrectomy with Billroth II reconstruction for early gastric cancer ($n = 14$). Control group: Patient's in-house relatives without a history of gastric surgery ($n = 8$)	Chemotherapy or radiotherapy 12 mo before inclusion. Gastric stump cancer. Usage of antibiotics, pro-, pre-, or synbiotics, H2-blocker, or PPI 1 month before inclusion. History of any gastrointestinal tract resections other than SGB2. Recurrence of gastric cancer, and current nongastric malignancies	Distal gastrectomy ($n = 14$). Types of reconstruction: Billroth II ($n = 14$)	Alpha diversity assessed by Shannon index was significantly decreased in gastrectomy patients. Median bacterial richness quantified by Chao1 index was similar. Beta diversity analysis showed significant differences between the microbiome composition of patients and controls; ANCOM identified the genus <i>Escherichia-Shigella</i> to be more abundant in gastrectomized patients. LEfSe attributed 11 additional genera to the gastrectomy group and 17 genera to the control (approximately half of them already have been implicated in PPI-induced or PPI-associated dysbiosis in previous reports). Increased abundance of <i>Escherichia-Shigella</i> , <i>Enterococcus</i> , <i>Streptococcus</i> , and other typical oral cavity bacteria (<i>Veillonella</i> , <i>Oribacterium</i> , and <i>Mogibacterium</i>) in gastrectomized patients	Fecal calprotectin marker was higher in gastrectomized patients. Fecal calprotectin was positively correlated with the abundance of <i>Streptococcus</i> and negatively correlated with the abundance of <i>Ruminococcaceae</i> , <i>Barnesiella</i> , <i>Ruminococcus 2</i> , <i>Ruminococcus 1</i> , and <i>Anaerostipes</i> . Abdominal discomfort was associated with a significantly higher abundance of <i>Holdemanella</i> and lower abundance of <i>Agathobacter</i> ; Diarrhea was associated with a significantly higher abundance of <i>Mogibacterium</i> and significantly lower abundance of <i>Ruminococcus 1</i> ; Bloating was associated with a significantly higher abundance of <i>Agathobacter</i> and <i>Streptococcus</i> . Patients who suffered from diarrhea also showed significantly higher serum levels of CRP and a trend to higher calprotectin level in stool compared with patients without diarrhea
Lin <i>et al</i> [28], 2018	CSS	Gastrectomy group: Patients with a history of distal gastrectomy	Age < 20 yr. Other underlying malignancies. Pre- and postoperative chemotherapy or chemoradiotherapy for GC. Other endocrine disorders such as DM,	Distal gastrectomy ($n = 111$). Types of reconstruction: Billroth	Significantly increased richness of gut microbiome after RYJ by Chao1 index. Tendency of increased richness of gut microbiome after SGB2 by Chao1	GC patients after subtotal gastrectomy with RYJ had a lower occurrence of metabolic syndrome and type II diabetes

for early GC (<i>n</i> = 111). Control group: Age and sex-matched subjects without a history of GI tract surgery (<i>n</i> = 344)	thyroid, pituitary, or adrenal disease. Moderate to severe cardiovascular, pulmonary, hepatic, or renal disease. Recurrent or uncured GC even after curative gastric surgery. The occurrence of complications after GC resection including anastomotic leakage, bleeding, intermittent intestinal adhesion, dumping syndrome, <i>etc.</i> Patients who received proton pump inhibitors, histamine-2 receptor antagonists, nonsteroidal anti-inflammatory drugs, antibiotics, or probiotics within one month of sample collection	II (<i>n</i> = 37); Roux-en-Y (<i>n</i> = 74)	index. Diversity assessed by Shannon index was similar in BII patients but higher in RYJG patients. LEfSe attributed 24 known genera, which were differently abundant between SGB2 and controls, and 43 genera differently abundant between RYJG and controls. <i>Oscillospira</i> , <i>Prevotella</i> , <i>Coproccoccus</i> , <i>Veillonella</i> , <i>Clostridium</i> , <i>Desulfovibrio</i> , <i>Anaerostipes</i> , <i>Slackia</i> , <i>Oxalobacter</i> , <i>Victivallis</i> , <i>Butyrivibrio</i> , <i>Sporobacter</i> , and <i>Campylobacter</i> were more abundant after subtotal gastrectomy irrespective of the type of reconstruction. Increased number of aero-tolerant <i>Streptococcus</i> and <i>Escherichia</i> in the RYJG group and <i>Klebsiella</i> in the SGB2 group. Increased abundance of typical oral microbiota (such as <i>Streptococcus</i> spp. and <i>Veillonella</i> spp.) in the gut microbiome of gastrectomized patients
---	--	---	---

CSS: Cross-sectional study; LS: Longitudinal study; GC: Gastric cancer; PPI: Proton pump inhibitors; SGB2: Subtotal gastrectomy with Billroth II reconstruction; CRP: C-reactive protein; RYJG: Subtotal gastrectomy with Roux-en-Y reconstruction.

bacterium in PPI-induced dysbiosis[27,41,43,46,47]. Previously, this bacterium was linked to intestinal inflammation and gut permeability in cirrhosis patients[40]. Similarly, *Streptococcus* was also associated with intestinal inflammation in gastrectomized patients[27]. Chronic intestinal inflammation may be involved in the pathogenesis of intermittent or permanent chronic diarrhea, which is present in up to 40% of long-term survivors after gastrectomy[3,48-50]. Previously post-gastrectomy diarrhea was attributed to vagotomy, endocrine hypofunction-related dyscoordination of the digestive tract, and abnormalities in the regulation of GI tract hormone secretion [50]. Although, as shown in IBD patients, chronic inflammation leads to damage of intestinal mucosa, dysregulation of intestinal ion transport, impaired and increased accessibility to the intestinal mucosa for pathogens[51]. Dysregulation of the expression and/or function of epithelial ion transporters and channels leads to electrolyte retention and water accumulation causing diarrhea[30]. Loss of epithelial barrier function contributes to diarrhea *via* a leak-flux mechanism, while mucosal penetration of enteric pathogens drives subsequent tissue damage[51]. Furthermore, patients suffering diarrhea after gastrectomy showed an increased abundance of *Mogibacterium* and decreased abundance of *Ruminococcus 1*[27]. *Mogibacterium* is increased in Crohn's patients[52] and decreased *Ruminococcus 1* was associated with diarrhea in an experimental porcine model[53].

Other common GI symptoms in gastrectomized patients are abdominal discomfort and bloating[27,48-50]. Both of these symptoms were associated with a decrease in *Agathobacter*[27]. These butyrate producers live in symbiosis with *Bifidobacteria*, which provides acetate as a substrate for butyrate production[54]. Abdominal discomfort was also, associated with increased abundance of *Holdemanella*[27]. There is a lack of evidence on the impact of *Holdemanella* on host health, although, their taxonomic family *Erysipelotrichaceae* contains highly immunogenic species and is associated with

pro-inflammatory conditions[27,55].

INCREASED OXYGEN LEVEL IN THE GUT AFTER GASTRECTOMY AND ITS IMPACT ON THE GUT MICROBIOME

The important anatomical and physiological changes in the GI tract after gastrectomy include increased oxygen in the distal part of the gut[56], which may provide an appropriate niche for aerobic and facultative anaerobic microbes. The studies on the gut microbiome after gastrectomy consistently showed an increased abundance of aero-tolerant microorganisms[27,28,34]. Erawijantari *et al*[6] demonstrated an increased abundance of aerobes (*Streptococcus*, *Enterococcus*) and facultative anaerobes (*Escherichia*, *Enterobacter*, and *Streptococcus*) in patients after gastrectomy. The study by Lin *et al*[28] showed a higher amount of aero-tolerant *Proteobacteria* phylum microorganisms including *Streptococcus*, *Escherichia*, and *Klebsiella*[28]. Similar, studies by Liang *et al*[29] and Horvath *et al*[27] demonstrated increased numbers of aerobes (*Streptococcus*) and facultative anaerobes (*Escherichia*) in patients after subtotal gastrectomy[27,29]. The increase in *Escherichia* was the most prominent difference between the microbiome of gastrectomy patients and controls documented in all studies[27-29,34]. *Escherichia* is a common protagonist in small intestinal bacterial overgrowth (SIBO)[57], which is a heterogeneous syndrome characterized by an increased number and/or abnormal type of bacteria in the small bowel[57]. SIBO occurs in the majority of patients after gastrectomy[58], and the clinical manifestation of this syndrome includes bloating, flatulence, abdominal discomfort, diarrhea, and abdominal pain[57], symptoms which are common in long-term survivors after gastrectomy[3,48-50].

Taken together, there is evidence associating GI symptoms after gastrectomy with specific changes in the gut microbiome composition, although further studies are warranted to confirm these findings and the exact mechanisms involved.

THE IMPACT OF BILIARY DIVERSION AFTER GASTRECTOMY ON THE GUT MICROBIOME

GI tract reconstruction following gastrectomy may lead to biliary diversion. The altered bile acid flow potentially stimulates the growth of bile acid-transforming bacteria[34]. The study by Erawijantari *et al*[6] extensively analyzed the fecal metabolomic profile and showed increased abundance of the secondary bile acid - deoxycholic acid (DCA) in gastrectomized patients[6]. Deconjugation of human primary bile acids and their subsequent biotransformation to secondary bile acids is a well-recognized function carried out by the human gut microbiome with its implications for human health[59]. The 7 α -dehydroxylation reaction has been described as the most quantitatively important process for the formation of secondary bile acids performed by the gut microbiome, specifically the bacteria that belong to the genus *Clostridium*[60]. The increased abundance of *Clostridium* following gastrectomy was confirmed in several studies[28,34]. Altered bile acid pool composition has been associated with several diseases including colorectal cancer[61,62], IBD, and metabolic syndrome[60].

DCA is a carcinogen in liver cancer and colorectal cancer[34,61,62]. Increased DCA in the intestine causes DNA damage through oxidative stress in intestinal epithelial cells and activates the epidermal growth factor receptor or Wnt pathways to promote colorectal cancer (CRC)[63]. These mechanisms may be responsible for the increased risk of metachronous CRC in GC patients[7,8]. Furthermore, the altered bile flow-induced gut microbiome changes were suggested as one of the potential mechanisms for the metabolic effect of gastrectomy[28]. Patients after subtotal gastrectomy with RYJ or B2 reconstruction were shown to have a lower body mass index or waist circumference compared to age and sex-matched healthy controls in the study by Lin *et al*[28]. Also, subtotal gastrectomy had some more positive effects such as higher serum high-density lipoprotein, lower total cholesterol, and triglyceride levels[28]. Only patients who underwent RYJ showed a lower prevalence of metabolic syndrome and type 2 diabetes[28]. The exact mechanisms linking subtotal gastrectomy with metabolic improvement remain unclear; however, some gut microbiome involving pathways were suggested[28]. They include: (1) The impact of the gut microbiome on the enteroendocrine function; (2) Altered bile acid flow, which is a

driver for changes in microbiome composition; and (3) Decreased levels of circulating lipopolysaccharides and altered bacterial components promoting hepatic insulin sensitivity[28].

LIMITATIONS OF THE CURRENT KNOWLEDGE AND PERSPECTIVES FOR FUTURE RESEARCH

The knowledge provided by the current studies has some limitations. First, most of the studies were cross-sectional design[27,28,34], and the only longitudinal study by Liang *et al*[29] was limited by a very small sample size and short follow-up[29]. Thus, there is a lack of data showing microbiome composition changes pre- and post-gastrectomy. Second, some studies included controls who were on gastric acid suppression medications or did not record the history of antibiotic use. These medications have a strong effect on the gut microbiome, thus, the impact of gastrectomy may have been underestimated[64]. Third, the current studies included patients with different extents of gastrectomy (total *vs* subtotal) and different types of reconstructions (B2, RYGJ, Billroth I). The impact of gastrectomy on the gut microbiome may be specific for the type of surgery; thus, future studies should clarify the impact of types of reconstruction after gastrectomy. Together, the present knowledge provides evidence on the impact of gastrectomy on the gut microbiome. These changes are driven by an altered environment in the GI tract, including loss of the gastric barrier, an increase in oxygenation levels in the distal gut, and biliary diversion. Further well-designed and appropriate size longitudinal studies are necessary to confirm this concept. These studies should incorporate data on health-related quality of life, especially on GI symptoms, metabolomics, and markers on intestinal inflammation and permeability to provide robust evidence on the impact of gastrectomy-induced dysbiosis on host health.

Several ongoing studies are already investigating gut microbiome changes through the GC treatment pathway. The LEGACY-2 trial (NCT04015466) is a large-scale international study aiming to study biological factors, including microbiome impact on clinical outcomes. The NeoChance trial (NCT04196465) is investigating the microbiome as a predictive/prognostic biomarker in patients who receive neoadjuvant immune checkpoint inhibitor IMC-001 for resectable GC. The NutriGIT (NCT04476082) study is investigating the nutritional status of patients with various GI cancers, including GC, and one of the study outcomes is changes in the gut microbiome. Together, these studies will increase the knowledge on microbiome changes through GC treatment and will highlight the impact of these changes on treatment outcomes. However, current studies are not designed to specifically investigate gastrectomy-induced dysbiosis; thus, such studies are still necessary.

The recent studies linked gut microbiome composition with the effectiveness of anti-cancer therapy[45,65]. An exploratory analysis of genus from the DELIVER trial showed that *Odoribacter* and *Veillonella* were associated with tumor response to Nivolumab in patients with advanced GC[45]. As mentioned previously, the abundance of typical oral bacteria-*Veillonella* increases following subtotal gastrectomy, due to the oralization phenomenon[27]. However, there is currently a lack of evidence to reliably characterize the impact of gastrectomy-induced dysbiosis on the effectiveness of anti-cancer therapy. As systemic therapy before and/or after surgery is the modern standard for GC, it would be of interest to investigate the association between gut microbiome and the efficacy of therapy in future studies.

CONCLUSION

Gastrectomy for GC impacts the composition of the gut microbiome. These changes are characterized by oralization, an increase in aero-tolerant bacteria (aerobes/facultative anaerobes), and increased abundance of bile acid-transforming bacteria. These changes are driven by an altered environment in the GI tract, including loss of the gastric barrier, an increase in oxygenation levels in the distal gut, and the biliary diversion after gastrectomy. Gastrectomy-induced dysbiosis is associated with host health. However, current evidence is limited; therefore, further longitudinal studies looking at different reconstructions of the GI tract are needed to confirm the concept and to investigate the mechanisms related to the impact of the gut microbiome on the health of GC patients.

REFERENCES

- 1 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: [30207593](#) DOI: [10.3322/caac.21492](#)]
- 2 **Stratilatovas E**, Baušys A, Baušys R, Sangaila E. Mortality after gastrectomy: a 10 year single institution experience. *Acta Chir Belg* 2015; **115**: 123-130 [PMID: [26021945](#) DOI: [10.1080/00015458.2015.11681081](#)]
- 3 **Yu W**, Park KB, Chung HY, Kwon OK, Lee SS. Chronological Changes of Quality of Life in Long-Term Survivors after Gastrectomy for Gastric Cancer. *Cancer Res Treat* 2016; **48**: 1030-1036 [PMID: [27004956](#) DOI: [10.4143/crt.2015.398](#)]
- 4 **Lee SS**, Chung HY, Kwon OK, Yu W. Quality of life in cancer survivors 5 years or more after total gastrectomy: a case-control study. *Int J Surg* 2014; **12**: 700-705 [PMID: [24866069](#) DOI: [10.1016/j.ijssu.2014.05.067](#)]
- 5 **Brenkman HJF**, Tegels JJW, Ruurda JP, Luyer MDP, Kouwenhoven EA, Draaisma WA, van der Peet DL, Wijnhoven BPL, Stoot JHMB, van Hillegersberg R; LOGICA Study Group. Factors influencing health-related quality of life after gastrectomy for cancer. *Gastric Cancer* 2018; **21**: 524-532 [PMID: [29067597](#) DOI: [10.1007/s10120-017-0771-0](#)]
- 6 **Erawijantari PP**, Mizutani S, Shiroma H, Shiba S, Nakajima T, Sakamoto T, Saito Y, Fukuda S, Yachida S, Yamada T. Influence of gastrectomy for gastric cancer treatment on faecal microbiome and metabolome profiles. *Gut* 2020; **69**: 1404-1415 [PMID: [31953253](#) DOI: [10.1136/gutjnl-2019-319188](#)]
- 7 **Ikeda Y**, Saku M, Kawanaka H, Nonaka M, Yoshida K. Features of second primary cancer in patients with gastric cancer. *Oncology* 2003; **65**: 113-117 [PMID: [12931016](#) DOI: [10.1159/000072335](#)]
- 8 **Eom BW**, Lee HJ, Yoo MW, Cho JJ, Kim WH, Yang HK, Lee KU. Synchronous and metachronous cancers in patients with gastric cancer. *J Surg Oncol* 2008; **98**: 106-110 [PMID: [18452218](#) DOI: [10.1002/jso.21027](#)]
- 9 **Bäumler AJ**, Sperandio V. Interactions between the microbiota and pathogenic bacteria in the gut. *Nature* 2016; **535**: 85-93 [PMID: [27383983](#) DOI: [10.1038/nature18849](#)]
- 10 **Clemente JC**, Ursell LK, Parfrey LW, Knight R. The impact of the gut microbiota on human health: an integrative view. *Cell* 2012; **148**: 1258-1270 [PMID: [22424233](#) DOI: [10.1016/j.cell.2012.01.035](#)]
- 11 **Bliss ES**, Whiteside E. The Gut-Brain Axis, the Human Gut Microbiota and Their Integration in the Development of Obesity. *Front Physiol* 2018; **9**: 900 [PMID: [30050464](#) DOI: [10.3389/fphys.2018.00900](#)]
- 12 **Shreiner AB**, Kao JY, Young VB. The gut microbiome in health and in disease. *Curr Opin Gastroenterol* 2015; **31**: 69-75 [PMID: [25394236](#) DOI: [10.1097/MOG.0000000000000139](#)]
- 13 **Zhan X**, Stamova B, Jin LW, DeCarli C, Phinney B, Sharp FR. Gram-negative bacterial molecules associate with Alzheimer disease pathology. *Neurology* 2016; **87**: 2324-2332 [PMID: [27784770](#) DOI: [10.1212/WNL.00000000000003391](#)]
- 14 **Zhao Y**, Jaber V, Lukiw WJ. Secretory Products of the Human GI Tract Microbiome and Their Potential Impact on Alzheimer's Disease (AD): Detection of Lipopolysaccharide (LPS) in AD Hippocampus. *Front Cell Infect Microbiol* 2017; **7**: 318 [PMID: [28744452](#) DOI: [10.3389/fcimb.2017.00318](#)]
- 15 **Everard A**, Belzer C, Geurts L, Ouwerkerk JP, Druart C, Bindels LB, Guiot Y, Derrien M, Muccioli GG, Delzenne NM, de Vos WM, Cani PD. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. *Proc Natl Acad Sci USA* 2013; **110**: 9066-9071 [PMID: [23671105](#) DOI: [10.1073/pnas.1219451110](#)]
- 16 **Li J**, Butcher J, Mack D, Stintzi A. Functional impacts of the intestinal microbiome in the pathogenesis of inflammatory bowel disease. *Inflamm Bowel Dis* 2015; **21**: 139-153 [PMID: [25248007](#) DOI: [10.1097/MIB.0000000000000215](#)]
- 17 **Mondot S**, Kang S, Furet JP, Aguirre de Carcer D, McSweeney C, Morrison M, Marteau P, Doré J, Leclerc M. Highlighting new phylogenetic specificities of Crohn's disease microbiota. *Inflamm Bowel Dis* 2011; **17**: 185-192 [PMID: [20722058](#) DOI: [10.1002/ibd.21436](#)]
- 18 **Wei B**, Su TT, Dalwadi H, Stephan RP, Fujiwara D, Huang TT, Brewer S, Chen L, Arditi M, Borneman J, Rawlings DJ, Braun J. Resident enteric microbiota and CD8⁺ T cells shape the abundance of marginal zone B cells. *Eur J Immunol* 2008; **38**: 3411-3425 [PMID: [19009526](#) DOI: [10.1002/eji.200838432](#)]
- 19 **Wu S**, Rhee KJ, Albesiano E, Rabizadeh S, Wu X, Yen HR, Huso DL, Brancati FL, Wick E, McAllister F, Housseau F, Pardoll DM, Sears CL. A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. *Nat Med* 2009; **15**: 1016-1022 [PMID: [19701202](#) DOI: [10.1038/nm.2015](#)]
- 20 **Karakan T**, Ozkul C, Küpeli Akkol E, Bilici S, Sobarzo-Sánchez E, Capasso R. Gut-Brain-Microbiota Axis: Antibiotics and Functional Gastrointestinal Disorders. *Nutrients* 2021; **13** [PMID: [33513791](#) DOI: [10.3390/nu13020389](#)]
- 21 **Liou AP**, Paziuk M, Luevano JM Jr, Machineni S, Turnbaugh PJ, Kaplan LM. Conserved shifts in the gut microbiota due to gastric bypass reduce host weight and adiposity. *Sci Transl Med* 2013; **5**: 178ra41 [PMID: [23536013](#) DOI: [10.1126/scitranslmed.3005687](#)]
- 22 **Palleja A**, Kashani A, Allin KH, Nielsen T, Zhang C, Li Y, Brach T, Liang S, Feng Q, Jørgensen NB, Bojsen-Møller KN, Dirksen C, Burgdorf KS, Holst JJ, Madsbad S, Wang J, Pedersen O, Hansen T,

- Arumugam M. Roux-en-Y gastric bypass surgery of morbidly obese patients induces swift and persistent changes of the individual gut microbiota. *Genome Med* 2016; **8**: 67 [PMID: [27306058](#) DOI: [10.1186/s13073-016-0312-1](#)]
- 23 **Zhang H**, DiBaise JK, Zuccolo A, Kudrna D, Braidotti M, Yu Y, Parameswaran P, Crowell MD, Wing R, Rittmann BE, Krajmalnik-Brown R. Human gut microbiota in obesity and after gastric bypass. *Proc Natl Acad Sci USA* 2009; **106**: 2365-2370 [PMID: [19164560](#) DOI: [10.1073/pnas.0812600106](#)]
- 24 **Karami R**, Kermansaravi M, Pishghroudsari M, Talebi M, Mohammadzadeh N, Pazouki A. Changes in gut microbial flora after Roux-en-Y gastric bypass and sleeve gastrectomy and their effects on post-operative weight loss. *Updates Surg* 2020 [PMID: [33067675](#) DOI: [10.1007/s13304-020-00900-9](#)]
- 25 **Xu G**, Song M. Recent advances in the mechanisms underlying the beneficial effects of bariatric and metabolic surgery. *Surg Obes Relat Dis* 2021; **17**: 231-238 [PMID: [33036939](#) DOI: [10.1016/j.soard.2020.08.028](#)]
- 26 **Sanchez-Carrillo S**, Ciordia S, Rojo D, Zubeldia-Varela E, Méndez-García C, Martínez-Martínez M, Barbas C, Ruiz-Ruiz S, Moya A, Garriga M, Salazar N, Botella-Carretero JI, Vega-Piñero B, de Los Reyes-Gavilán CG, Del Campo R, Ferrer M. A body weight loss- and health-promoting gut microbiota is established after bariatric surgery in individuals with severe obesity. *J Pharm Biomed Anal* 2021; **193**: 113747 [PMID: [33217711](#) DOI: [10.1016/j.jpba.2020.113747](#)]
- 27 **Horvath A**, Bausys A, Sabaliauskaite R, Stratilaitovas E, Jarmalaite S, Schuetz B, Stiegler P, Bausys R, Stadlbauer V, Strupas K. Distal Gastrectomy with Billroth II Reconstruction is Associated with Oralization of Gut Microbiome and Intestinal Inflammation: A Proof-of-Concept Study. *Ann Surg Oncol* 2021; **28**: 1198-1208 [PMID: [32504369](#) DOI: [10.1245/s10434-020-08678-1](#)]
- 28 **Lin XH**, Huang KH, Chuang WH, Luo JC, Lin CC, Ting PH, Young SH, Fang WL, Hou MC, Lee FY. The long term effect of metabolic profile and microbiota status in early gastric cancer patients after subtotal gastrectomy. *PLoS One* 2018; **13**: e0206930 [PMID: [30395589](#) DOI: [10.1371/journal.pone.0206930](#)]
- 29 **Liang W**, Yang Y, Wang H, Yu X, Lu Y, Shen S, Teng L. Gut microbiota shifts in patients with gastric cancer in perioperative period. *Medicine (Baltimore)* 2019; **98**: e16626 [PMID: [31464899](#) DOI: [10.1097/MD.00000000000016626](#)]
- 30 **Heiman ML**, Greenway FL. A healthy gastrointestinal microbiome is dependent on dietary diversity. *Mol Metab* 2016; **5**: 317-320 [PMID: [27110483](#) DOI: [10.1016/j.molmet.2016.02.005](#)]
- 31 **Turnbaugh PJ**, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, Sogin ML, Jones WJ, Roe BA, Affourtit JP, Egholm M, Henrissat B, Heath AC, Knight R, Gordon JI. A core gut microbiome in obese and lean twins. *Nature* 2009; **457**: 480-484 [PMID: [19043404](#) DOI: [10.1038/nature07540](#)]
- 32 **Larsen N**, Vogensen FK, van den Berg FW, Nielsen DS, Andreassen AS, Pedersen BK, Al-Soud WA, Sørensen SJ, Hansen LH, Jakobsen M. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS One* 2010; **5**: e9085 [PMID: [20140211](#) DOI: [10.1371/journal.pone.0009085](#)]
- 33 **Kowalska-Duplaga K**, Gosiewski T, Kapusta P, Sroka-Oleksiak A, Wędrychowicz A, Pieczarkowski S, Ludwig-Słomczyńska AH, Wołkow PP, Fyderek K. Differences in the intestinal microbiome of healthy children and patients with newly diagnosed Crohn's disease. *Sci Rep* 2019; **9**: 18880 [PMID: [31827191](#) DOI: [10.1038/s41598-019-55290-9](#)]
- 34 **Dhakan DB**, Maji A, Sharma AK, Saxena R, Pulikkan J, Grace T, Gomez A, Scaria J, Amato KR, Sharma VK. The unique composition of Indian gut microbiome, gene catalogue, and associated fecal metabolome deciphered using multi-omics approaches. *Gigascience* 2019; **8** [PMID: [30698687](#) DOI: [10.1093/gigascience/giz004](#)]
- 35 **Huang L**, Xu AM, Li TJ, Han WX, Xu J. Should peri-gastrectomy gastric acidity be our focus among gastric cancer patients? *World J Gastroenterol* 2014; **20**: 6981-6988 [PMID: [24944492](#) DOI: [10.3748/wjg.v20.i22.6981](#)]
- 36 **Rieu PN**, Jansen JB, Hopman WP, Joosten HJ, Lamers CB. Effect of partial gastrectomy with Billroth II or Roux-en-Y anastomosis on postprandial and cholecystokinin-stimulated gallbladder contraction and secretion of cholecystokinin and pancreatic polypeptide. *Dig Dis Sci* 1990; **35**: 1066-1072 [PMID: [2390921](#) DOI: [10.1007/BF01537576](#)]
- 37 **Jepson K**, Johnston D. Effect of vagotomy on human gastric acid secretion stimulated by gastrin pentapeptide and by histalog. *Gastroenterology* 1968; **55**: 665-669 [PMID: [5727781](#)]
- 38 **Martinsen TC**, Bergh K, Waldum HL. Gastric juice: a barrier against infectious diseases. *Basic Clin Pharmacol Toxicol* 2005; **96**: 94-102 [PMID: [15679471](#) DOI: [10.1111/j.1742-7843.2005.pto960202.x](#)]
- 39 **Carboni M**, Guadagni S, Pistoia MA, Amicucci G, Tuscano D, Negro P, Smith PL, Walters CL. The microflora of the gastric juice after Billroth I and Billroth II partial gastrectomy. *Scand J Gastroenterol* 1986; **21**: 461-470 [PMID: [3726452](#) DOI: [10.3109/00365528609015163](#)]
- 40 **Horvath A**, Rainer F, Bashir M, Leber B, Schmerboeck B, Klymiuk I, Groselj-Strele A, Durdevic M, Freedberg DE, Abrams JA, Fickert P, Stiegler P, Stadlbauer V. Biomarkers for oralization during long-term proton pump inhibitor therapy predict survival in cirrhosis. *Sci Rep* 2019; **9**: 12000 [PMID: [31427714](#) DOI: [10.1038/s41598-019-48352-5](#)]
- 41 **Imhann F**, Bonder MJ, Vich Vila A, Fu J, Mujagic Z, Vork L, Tigchelaar EF, Jankipersadsing SA, Cenit MC, Harmsen HJ, Dijkstra G, Franke L, Xavier RJ, Jonkers D, Wijmenga C, Weersma RK,

- Zhernakova A. Proton pump inhibitors affect the gut microbiome. *Gut* 2016; **65**: 740-748 [PMID: 26657899 DOI: 10.1136/gutjnl-2015-310376]
- 42 **Bajaj JS**, Cox JJ, Betrapally NS, Heuman DM, Schubert ML, Ratneswaran M, Hylemon PB, White MB, Daita K, Noble NA, Sikaroodi M, Williams R, Crossey MM, Taylor-Robinson SD, Gillevet PM. Systems biology analysis of omeprazole therapy in cirrhosis demonstrates significant shifts in gut microbiota composition and function. *Am J Physiol Gastrointest Liver Physiol* 2014; **307**: G951-G957 [PMID: 25258407 DOI: 10.1152/ajpgi.00268.2014]
- 43 **Jackson MA**, Goodrich JK, Maxan ME, Freedberg DE, Abrams JA, Poole AC, Sutter JL, Welter D, Ley RE, Bell JT, Spector TD, Steves CJ. Proton pump inhibitors alter the composition of the gut microbiota. *Gut* 2016; **65**: 749-756 [PMID: 26719299 DOI: 10.1136/gutjnl-2015-310861]
- 44 **Aas JA**, Paster BJ, Stokes LN, Olsen I, Dewhirst FE. Defining the normal bacterial flora of the oral cavity. *J Clin Microbiol* 2005; **43**: 5721-5732 [PMID: 16272510 DOI: 10.1128/JCM.43.11.5721-5732.2005]
- 45 **Sunakawa Y**, Matoba R, Inoue E, Sakamoto Y, Kawabata R, Ishiguro A, Akamaru Y, Kito Y, Takahashi M, Matsuyama J, Yabusaki H, Makiyama A, Suzuki T, Tsuda M, Yasui H, Kawakami H, Muro K, Nakajima TE, Ichikawa W, Fujii M. Genomic pathway of gut microbiome to predict efficacy of nivolumab in advanced gastric cancer: DELIVER trial (JACCRO GC-08). *J Clin Oncol* 2021; **39**: 161-161 [DOI: 10.1200/JCO.2021.39.3_suppl.161]
- 46 **Tsuda A**, Suda W, Morita H, Takanashi K, Takagi A, Koga Y, Hattori M. Influence of Proton-Pump Inhibitors on the Luminal Microbiota in the Gastrointestinal Tract. *Clin Transl Gastroenterol* 2015; **6**: e89 [PMID: 26065717 DOI: 10.1038/ctg.2015.20]
- 47 **Clooney AG**, Bernstein CN, Leslie WD, Vagianos K, Sargent M, Laserna-Mendieta EJ, Claesson MJ, Targownik LE. A comparison of the gut microbiome between long-term users and non-users of proton pump inhibitors. *Aliment Pharmacol Ther* 2016; **43**: 974-984 [PMID: 26923470 DOI: 10.1111/apt.13568]
- 48 **Karanicolas PJ**, Graham D, Gönen M, Strong VE, Brennan MF, Coit DG. Quality of life after gastrectomy for adenocarcinoma: a prospective cohort study. *Ann Surg* 2013; **257**: 1039-1046 [PMID: 23665970 DOI: 10.1097/SLA.0b013e31828c4a19]
- 49 **Kim AR**, Cho J, Hsu YJ, Choi MG, Noh JH, Sohn TS, Bae JM, Yun YH, Kim S. Changes of quality of life in gastric cancer patients after curative resection: a longitudinal cohort study in Korea. *Ann Surg* 2012; **256**: 1008-1013 [PMID: 23154395 DOI: 10.1097/SLA.0b013e31827661e9]
- 50 **Aoki T**, Yamaji I, Hisamoto T, Sato M, Matsuda T. Irregular bowel movement in gastrectomized subjects: bowel habits, stool characteristics, fecal flora, and metabolites. *Gastric Cancer* 2012; **15**: 396-404 [PMID: 22282135 DOI: 10.1007/s10120-011-0129-y]
- 51 **Anbazhagan AN**, Priyamvada S, Alrefai WA, Dudeja PK. Pathophysiology of IBD associated diarrhea. *Tissue Barriers* 2018; **6**: e1463897 [PMID: 29737913 DOI: 10.1080/21688370.2018.1463897]
- 52 **Qiu Z**, Yang H, Rong L, Ding W, Chen J, Zhong L. Targeted Metagenome Based Analyses Show Gut Microbial Diversity of Inflammatory Bowel Disease patients. *Indian J Microbiol* 2017; **57**: 307-315 [PMID: 28904415 DOI: 10.1007/s12088-017-0652-6]
- 53 **Yang Q**, Huang X, Wang P, Yan Z, Sun W, Zhao S, Gun S. Longitudinal development of the gut microbiota in healthy and diarrheic piglets induced by age-related dietary changes. *Microbiologyopen* 2019; **8**: e923 [PMID: 31496126 DOI: 10.1002/mbo3.923]
- 54 **Rivière A**, Gagnon M, Weckx S, Roy D, De Vuyst L. Mutual Cross-Feeding Interactions between *Bifidobacterium longum* subsp. *longum* NCC2705 and *Eubacterium rectale* ATCC 33656 Explain the Bifidogenic and Butyrogenic Effects of Arabinoxylan Oligosaccharides. *Appl Environ Microbiol* 2015; **81**: 7767-7781 [PMID: 26319874 DOI: 10.1128/AEM.02089-15]
- 55 **Kaakoush NO**. Insights into the Role of Erysipelotrichaceae in the Human Host. *Front Cell Infect Microbiol* 2015; **5**: 84 [PMID: 26636046 DOI: 10.3389/fcimb.2015.00084]
- 56 **Celiker H**. A new proposed mechanism of action for gastric bypass surgery: Air hypothesis. *Med Hypotheses* 2017; **107**: 81-89 [PMID: 28915970 DOI: 10.1016/j.mehy.2017.08.012]
- 57 **Sachdev AH**, Pimentel M. Gastrointestinal bacterial overgrowth: pathogenesis and clinical significance. *Ther Adv Chronic Dis* 2013; **4**: 223-231 [PMID: 23997926 DOI: 10.1177/2040622313496126]
- 58 **Paik CN**, Choi MG, Lim CH, Park JM, Chung WC, Lee KM, Jun KH, Song KY, Jeon HM, Chin HM, Park CH, Chung IS. The role of small intestinal bacterial overgrowth in postgastrectomy patients. *Neurogastroenterol Motil* 2011; **23**: e191-e196 [PMID: 21324050 DOI: 10.1111/j.1365-2982.2011.01686.x]
- 59 **Heinken A**, Ravcheev DA, Baldini F, Heirendt L, Fleming RMT, Thiele I. Systematic assessment of secondary bile acid metabolism in gut microbes reveals distinct metabolic capabilities in inflammatory bowel disease. *Microbiome* 2019; **7**: 75 [PMID: 31092280 DOI: 10.1186/s40168-019-0689-3]
- 60 **Staley C**, Weingarden AR, Khoruts A, Sadowsky MJ. Interaction of gut microbiota with bile acid metabolism and its influence on disease states. *Appl Microbiol Biotechnol* 2017; **101**: 47-64 [PMID: 27888332 DOI: 10.1007/s00253-016-8006-6]
- 61 **Yachida S**, Mizutani S, Shiroma H, Shiba S, Nakajima T, Sakamoto T, Watanabe H, Masuda K, Nishimoto Y, Kubo M, Hosoda F, Rokutan H, Matsumoto M, Takamaru H, Yamada M, Matsuda T, Iwasaki M, Yamaji T, Yachida T, Soga T, Kurokawa K, Toyoda A, Ogura Y, Hayashi T, Hatakeyama M, Nakagama H, Saito Y, Fukuda S, Shibata T, Yamada T. Metagenomic and metabolomic analyses

- reveal distinct stage-specific phenotypes of the gut microbiota in colorectal cancer. *Nat Med* 2019; **25**: 968-976 [PMID: [31171880](#) DOI: [10.1038/s41591-019-0458-7](#)]
- 62 **Wirbel J**, Pyl PT, Kartal E, Zych K, Kashani A, Milanese A, Fleck JS, Voigt AY, Palleja A, Ponnudurai R, Sunagawa S, Coelho LP, Schrotz-King P, Vogtmann E, Habermann N, Niméus E, Thomas AM, Manghi P, Gandini S, Serrano D, Mizutani S, Shiroma H, Shiba S, Shibata T, Yachida S, Yamada T, Waldron L, Naccarati A, Segata N, Sinha R, Ulrich CM, Brenner H, Arumugam M, Bork P, Zeller G. Meta-analysis of fecal metagenomes reveals global microbial signatures that are specific for colorectal cancer. *Nat Med* 2019; **25**: 679-689 [PMID: [30936547](#) DOI: [10.1038/s41591-019-0406-6](#)]
- 63 **Liu L**, Dong W, Wang S, Zhang Y, Liu T, Xie R, Wang B, Cao H. Deoxycholic acid disrupts the intestinal mucosal barrier and promotes intestinal tumorigenesis. *Food Funct* 2018; **9**: 5588-5597 [PMID: [30339173](#) DOI: [10.1039/c8fo01143e](#)]
- 64 **Vich Vila A**, Collij V, Sanna S, Sinha T, Imhann F, Bourgonje AR, Mujagic Z, Jonkers DMAE, Masclee AAM, Fu J, Kurilshikov A, Wijmenga C, Zhernakova A, Weersma RK. Impact of commonly used drugs on the composition and metabolic function of the gut microbiota. *Nat Commun* 2020; **11**: 362 [PMID: [31953381](#) DOI: [10.1038/s41467-019-14177-z](#)]
- 65 **Ma W**, Mao Q, Xia W, Dong G, Yu C, Jiang F. Gut Microbiota Shapes the Efficiency of Cancer Therapy. *Front Microbiol* 2019; **10**: 1050 [PMID: [31293523](#) DOI: [10.3389/fmicb.2019.01050](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

