ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Review Article

Do Cholecystectomy and Appendicectomy Damage the Intestinal Microbiota?

Álvaro Zamudio Tiburcio[1]*, Héctor Bermúdez Ruiz[2], Silverio Alonso López[3] and Pedro Antonio Reyes López[4]

[1]Department of Gastroenterology, Intestinal Microbiota Transplantation, Medical Specialties, Naples Unit, Mexico

[2]Endoscopy Service, Oncology Hospital, National Medical Center, XXI Century, Mexican Social Security Institute, Hospital Trinidad, Mexico City, Mexico

[3]Department of Urologist, Chairman Medical Specialties Naples in Mexico City, Mexico

[4]Immunologist, Rheumatologist, National Institute of Cardiology "I. Chávez", Mexico City, Mexico

***Corresponding Author:** Álvaro Zamudio Tiburcio, Department of Gastroenterology, Intestinal Microbiota Transplantation, Medical Specialties, Naples Unit, Mexico.

Received: March 14, 2024; Published: March 21, 2024

Abstract

This review is not intended to determine which is the best procedure, surgical or medical, in two of the most frequent surgeries in gastroenterology, but rather the objective is to assist in the improvement of the microbiome, in order to avoid the processes added morbidities, as well as determining some pre-, trans- or postoperative management that helps patients who have suffered one of these two conditions.

It is known that the impact that alterations of the gut microbiota (Dysbiosis-dysbacteriosis) or vice versa, generate inflammatory processes in other areas, some more intense than others, but all of them produce minimal, regular or maximum damage. Thus, we see that cholelithiasis can appear in inflammatory bowel disease, both in the gallbladder and in the bile duct and intrahepatic.

We will evaluate in unison the two processes cholecystectomy and appendectomy, and the changes in the various phyla that these produce, giving rise to probable parallel treatments.

In principle, we must understand the impact generated by more than nine million genes and accept that microorganisms, for the most part, are not our enemies, rather our allies, in a very interesting pairing (symbiosis), which we must care for and protect, since that this action fundamentally translates health.

We consider the use of biotics in both processes and point out the care that must be taken with these products, since some of them can also cause complications, as well as knowing which would be the best biotic and considering that they are foreign bodies, which do not they necessarily impact the digestive tract, as one would like.

We conclude with the consideration of how useful or not, the gut microbiota transplant could be and, everything that is missing, so that this methodology has a space for action.

Keywords: *Cholecystectomy (COL); Appendicectomy (AP); Gut Microbiota (GM); Microbiome (M); Intestinal Dysbiosis (ID)*

Introduction

For more than 50 years, surgeons from various countries have advocated conservative treatment of gallbladder inflammation in some stages of the condition [1]. The determination is complicated, given the avalanche of information about the microbiome (M): "Microorganisms, in community (bacteria, fungi, viruses, etc.) that exist in a particular environment of human beings". This large contingent is estimated at hundreds of bacterial groups and more than nine million genes, including three billion cells [2].

Something similar can be said about appendectomy (AP), since the avalanche of microbiological information forces us to be very cautious in the proposals.

We see, in cholecystectomy (COL) that the elimination of M linked to old age and bacteria in relation to bile acids, as generators of colorectal cancer [3]. Not being rare, concern about the presence of non-alcoholic fatty liver.

Microbiota in the gallbladder and appendix, normal: The biliary microbiota has been described in some hepato-biliary diseases. One of them, using sequencing analysis based on the 16S rRNA gene; they find *Firmicutes, Bacteroidetes, Actinobacteria* and *Proteobacteria*; with differences in relative abundance. In relation to the healthy appendix, its microbiota is very similar to that of the colon, mainly finding aerobic bacteria *Escherichia coli* (77%), and anaerobic *Bacteroides fragilis* (80%). With participating function in the immune system, secreting IgA [4].

Microbiota in the gallbladder and appendix, with pathology: *Bacteroidaceae, Prevotellaceae, Porphyromonadaceae* and *Veillonellaceae* are observed in people with cholelithiasis [5]. Watanabe S and his group [6], show in patients with brain death that bile cultures are negative, while the determination of the 16S ribosome obtains bacteria in all cases. These are: *Firmicutes, Proteobacteria, Actinobacteria* and *Anaerobacillus* (58.62%), *Delftia* (87.63%), *Bacillus, Ralstonia, Ochrobactrum, Acidovorax* and *Curvibacter*.

In acute appendicitis, described since 1886 by Dr. Reginald Fitz, *Firmicutes* predominate (43%), followed by *Proteobacteria* (22%), *Bacteroidetes* (20%) and *Actinobacteria* (10%). The metabolomic analysis showed that patients with healthy and diseased gallbladders have different metabolic profiles. Oh SJ and his collaborators [7] observed that the presence of *Campylobacter jejuni* and not other *Campylobacters*, were higher in acute appendicitis. Suggesting that management with specific antibiotics could be appropriate in uncomplicated appendicitis. While Guinane CM [8] and his group, point out that the appendix is a dam to reforest the digestive tract, in case of deficiency. Likewise, they found that *Firmicutes* is the main phylo, and the additional complementary sequences were: *Proteobacteria, Bacteroidetes*, *Actinobacteria* and *Fusobacteria*. Dan WY and his group [9] point out that gastrointestinal M (microorganisms and metabolites) could be involved in cholelithiasis, encouraging cholelithogenesis, by regulating the metabolism of bile acids. Finally, Wang W's group [10] refers to the importance of GM in achieving homeostasis and metabolism.

Even though acute cholecystitis is best treated with surgery, it can be managed conservatively [11] when associated with lack of stones.

On the other hand, acute appendicitis consists of two processes, one that presents with necrosis, causing perforation and consequently appendiceal abscess, and the other that is not complicated [12]; The processes depend on the microbiota involved. The complicated one is determined by the oral microbiota (*Fusobacterium* spp, *Porphyromonas* and *Parvimonas*) and the second by GM. Therefore, it is possible that determining a good diagnosis of M could determine the specific indication.

Dysbiosis in inflammations of the gallbladder and appendix: Removal of the gallbladder and vermicular appendix alters GM, which increases the risk of another condition. Occur, through dysbiosis: "Breakdown of the balance of the ecosystem, affecting the resilience capacities of our microorganisms, ceasing to fulfill their functions, affecting health" [13]. The associated mechanisms have been related

to GM dysbiosis. Cholecystectomy causes changes in bile acid constitution and bile secretion as bile acids interact with IM bidirectionally. For dysbiosis to exist, the participation of bile acids is required. Not only does dysbiosis generate cholecystitis and appendicitis, it can also appear inflammatory bowel disease, irritable bowel syndrome and even colorectal cancer [14].

Dysbiosis acts at the beginning and development of the inflammatory and infectious process in acute appendicitis. Observing *Clostridium* and *Prevotella*, in greater numbers than *Streptococci*. Sánchez-Alcoholado L and his team [15] point out that in bariatric accidental AP, they found low diversity rates, with increased levels of *Bilophila, Odoribacter, Butyricimonas* and *Faecalibacterium*, while *Lachnobacterium* increased. Likewise, they detected that *Butyricimonas* and *Odoribacter* are related to the regulation of insulin.

Cai S and her associates [16] point out that there is bacterial and fungal alteration (five years, in the case of fungi), in the postoperative period of AP, without changes in alpha diversity, more so in beta. In addition to an increase in microorganisms that produce SCFA, especially butyrate, acetic and propionic acid.

The study by Shi., *et al*. [17], identifies the following bacteria, after AP, *B. vulgatus, B. fragilis, P. ruminicola*, *Veillonella dispar, P. dentalis, P. fusca*, and *P. denticola*, related to tumorigenesis and intestinal inflammation, confirming that this tumorigenesis has to do with AP.

Immunological alterations in cholecystitis and appendicitis: The effects of inflammatory mediators in cholecystitis and appendicitis are known. Within them, chemokines, cytosines and prostaglandins appear [18]. The hyperdevelopment of *Prevotella* and other microorganisms usually generates an inflammatory response, releasing mediators that activate the immune system [19].

It must be remembered that the appendix has lymphoid tissue, which confirms its immunological vocation, in the digestive system, pushing the production of B cells and disrupting immune function. In this, GM maintains intestinal homeostasis and immune functions and through SCFA, regulates immunity, protection of the intestinal mucosa, as well as inflammation and supplies epithelial cells. In addition, there is release of IgA [20].

The development of appendiceal lymphoid tissue is independent, increasing primary antibodies and maturing T and B lymphocyte cells. Enterocytes, columnar epithelia and goblet cells complement the lamina propria and the muscular area of the appendiceal mucosa, while plasma cells and macrophages generate IgA and IgG. CD8+ T regulatory lymphocytes are located the same as in the cecum, in the appendix [21].

In both cholecystitis and colorectal cancer, changes in immunological studies appear, especially interleukin-2-A in gallbladder inflammation [22].

The effects of laparoscopic procedures have also been referred to, thus we see that in COL it is noted that both the interleukin-18 (IL-18) and monocyte chemotactic protein-1 scale increase significantly, determining that both markers are sensitive, in these cases [23]. Fact, which is reiterated by Boo YJ., *et al*. [24]. In the case of AP Simon P and his team, they found significant determinations, and even added, determination of C-reactive protein, interleukin (IL)-6, tumor necrosis factor (TNF)-α, sTNF-R, IL- 1Ra, sIL-2R and IL-8 [25].

The new evidence, which appears by deepening the knowledge of the M and the immune system, has led to a more exact understanding of the function of the appendix (Refuge for beneficial microorganisms), pointing out that AP increases the risk of other morbid processes appearing (*C. difficile*, recurrent colitis, and others, which have to do with the modification of M [26].

What are the indications for no cholecystectomy and no appendectomy? We will start by saying what the indications of both processes are. Regarding COL, they are: Cancer, trauma, acute cholecystitis and lithiasis. And no COL in the majority of asymptomatic lithiasis. While laparoscopic AP is used mainly in pregnancies, pediatrics and the elderly, obese. And non-AP in patients who improve with

antibiotics, mild cases or if perforation and abscess. And they present a high operative risk [27-29]. Collard M., *et al*. they point out that the COVID-19 crisis forced France to consider appendicitis - in some cases - as something that has to be postponed, with good, rational criteria. Above all, excellent high-quality studies suggest management with antibiotic therapy. However, it is good to add the negative effect that antibiotics have on GM [30].

Parallel diseases caused by cholecystectomy and appendectomy: These pathologies include: colorectal cancer, metabolic abnormalities, gastritis due to bile reflux, non-alcoholic fatty liver, liver cirrhosis due to progression of the condition, insulin resistance, nutrient overload and inflammation. Obesity Diabetes and those that coincide with metabolic syndrome. *Enterobacteriaceae*, including *Klebsiella*, were detected in gallbladder carcinogenesis [31-33]. Finally, there are suspicions that Parkinson's Disease has a strong link with AP. And in this relationship, abundance of *Enterobacteriaceae* is observed [34]. On the other hand, it is determined that dysbiosis is the inducing phenomenon of the various pathologies observed in the postoperative period of COL and AP [35]. Highlighting the significant differences between the composition of the colon and the appendix.

Biotics

Probiotics: By regulating adaptive and innate immune systems, influencing immune cells (dendritic cells, B and T lymphocytes and macrophages), they generate a desirable positive effect; This effect was corroborated by Maldonado and his team [36], when they found that *Lactobacillus casei* CRL 431 and *Lactobacillus paracasei* CNCM I-1518 influence the immune response, through impact on macrophages, located in the spleen, Peyer's patches and peritoneum. Additionally, probiotics mediate immunomodulation and often regulate gene expression. Therefore, probiotics have potential in acute appendicitis, even though more research is required. Petruzziello C., *et al*. [37]. They comment that probiotics can be added therapy, with favorable results, in acute appendicitis, since they affect inflammation, positively impacting the mucosa and, on the immune systems, both adaptive and innate, and can reduce complications postoperative. Don't forget that these biotics can modulate GM. Likewise, prevent the generation of gallstones, by modifying bile acids (deoxycholic acid), reducing intestinal movement. Manifest situations in bariatric surgery itself [38].

Prebiotics: These biotics are analyzed, thus we see that in a study of 185,713 high-quality sequence reads in feces, *Escherichia coli* was the most found, as a pathogenic microorganism, in addition to *Klebsiella* spp, *Citrobacter freundii, Clostridium perfringens* and *Enterobacter cloacae*. Considering the positive impact of the control of *Enterobacteriaceae*, to improve infection [39].

Early nutrition accompanied by prebiotics causes a better postoperative period. IL-12 decreased postoperatively and increased until day 8 [40].

Symbiotics: Postoperative infections treated with symbiotics are reduced by increasing the impact of fecal SCFA, since they prevent the translocation of pathogenic microorganisms [40]. Therefore, the use of *Bifidobacterium* and *Lactobacillus* is correct, since they decrease after an invasive abdominal surgical procedure. Therefore, the improvement of the M and the intestinal barrier in the preoperative period is significant. Getting even better if we add lactic acid bacteria. IL-12 decreased postoperatively and increased until day 8 [41].

However, we must be cautious in the administration of microorganisms, since it has been found that *Lactobacillus paracasei* can cause meningitis, endocarditis, pancreatitis, cholecystitis and even peritonitis [42].

Is intestinal microbiota transplant useful in gallbladder and appendicular processes? If *Clostridium difficile* infection, especially recurrent, appears as a complication in acute appendicitis, the fecal microbiota transplant should not wait. Above all, AP can increase the severity of the infection [43].

The Gastroenterology Association of the United States of America determines in its 2024 guidelines that transplantation may be useful in the following diseases: *Clostridioides difficile*; severe to fulminant *C. difficile* infection; inflammatory bowel diseases, including pouchitis; and irritable bowel syndrome (Clinical trials). The AGA points out; "In mildly or moderately immunocompromised adults with recurrent *C. difficile* infection, the select use of conventional fecal microbiota transplantation is suggested" [44].

Conclusion

- Current knowledge of M makes us more cautious regarding considerations of both the gallbladder and the vermiform appendix.
- We must consider M as our ally.
- Dysbiosis is the cause of the parallel diseases seen in COL and AP.
- Immune alterations occur in both processes and can help us in parallel management.
- The use of biotics pre, tans and post-surgery can be beneficial.

Bibliography

1. Coldrey E. "Treatment of acute appendicitis". *British Medical Journal* 2.5007 (1956): 1458-1461.
2. Moreno MC., *et al*. "Microbioma humano". *Revista De la Facultad de Medicina de la UNAM* 61.6 (2018): 7-19.
3. Jiang X., *et al*. "Cholecystectomy promotes the development of colorectal cancer by the alternation of bile acid metabolism and the gut microbiota". *Frontiers in Medicine (Lausanne)* 9 (2022): 1000563.
4. Aguilar Salinas P and Domínguez Garibaldi FJ. "Acute appendicitis in adults. Review". *Ciencia UG* 2.3 (2012): 21-28.
5. Molinero N., *et al*. "The human gallbladder microbiome is related to the physiological state and the biliary metabolic profile". *Microbiome* 7.1 (2019): 100.
6. Watanabe S., *et al*. "Bile collected from the normal gallbladder of patients during surgery has simple bacterial flora". *Cureus* 14.6 (2022): e25681.
7. Oh SJ., *et al*. "Acute appendicitis is associated with appendiceal microbiome changes including elevated *Campylobacter jejuni* levels". *BMJ Open Gastroenterology* 7.1 (2020): e000412.
8. Guinane CM., *et al*. "Microbial composition of human appendices from patients following appendectomy". *mBio* 4.1 (2013): e00366-12.
9. Dan WY., *et al*. "Gastrointestinal microbiome and cholelithiasis: Current status and perspectives". *World Journal of Gastroenterology* 29.10 (2023): 1589-1601.
10. Wang W., *et al*. "Cholecystectomy damages aging-associated intestinal microbiota construction". *Frontiers in Microbiology* 9 (2018): 1402.
11. Jones MW., *et al*. "Acute cholecystitis". National Library of Medicine (2023).
12. Blohs M., *et al*. "Acute appendicitis manifests as two microbiome state types with oral pathogens influencing severity". *Gut Microbes* 5.1 (2023): 2145845.
13. Chen J., *et al*. "The gallbladder and vermiform appendix influence the assemblage of intestinal microorganisms". *Future Microbiology* 15 (2020): 541-555.

14. Quaglio AEV., *et al*. "Gut microbiota, inflammatory bowel disease and colorectal cancer". *World Journal of Gastroenterology* 28.30 (2022): 4053-4060.

15. Sánchez-Alcoholado L., *et al*. "Incidental prophylactic appendectomy is associated with a profound microbial dysbiosis in the long-term". *Microorganisms* 8.4 (2020): 609.

16. Cai S., *et al*. "Appendicectomy is associated with alteration of human gut bacterial and fungi communities". *Frontiers in Microbiology* 12 (2021): 724980.

17. Shi F., *et al*. "Altered gut microbiome composition by appendectomy contributes to colorectal cancer". *Oncogene* 42 (2023): 530-540.

18. Elwan TH., *et al*. "Unveiling the role of inflammatory mediators and gut microbiome in appendicitis: types and applications in clinical scoring". *Advanced Gut & Microbiome Research* (2023): 1080495.

19. Wang D., *et al*. "Comparison of the effects of acute appendicitis and chronic cholecystitis on intestinal mucosal function during surgery". *Cureus* 14.11 (2022): e30953.

20. Wu HJ and Wu E. "The role of gut microbiota in immune homeostasis and autoimmunity". *Gut Microbes* 3.1 (2012): 4-14.

21. Vitetta L., *et al*. "The vermiform appendix: an immunological organ Sustaining a microbiome inoculum". *Clinical Science (London)* 133.1 (2019): 1-8.

22. Asenjo BDA. "Comportamiento de ciertos parámetros inmunológicos, marcadores tumorales y eritropoyetina en colecistitis aguda y cáncer colorectal". Tesis. Universidad Valladolid, España (1997).

23. Li F., *et al*. "Immunological effects of laparoscopic and open cholecystectomy". *Journal of International Medical Research* 38.6 (2010): 2077-2083.

24. YJ Boo., *et al*. "Systemic immune response after open versus laparoscopic cholecystectomy in acute cholecystitis: A prospective randomized study". *Scandinavian Journal of Clinical and Laboratory Investigation* 67.2 (2007): 207-214.

25. Simon P., *et al*. "Inflammatory response is no different in children randomized to laparoscopic or open appendectomy". *Journal of Laparoendoscopy and Advances Surgical Techniques* 19.s1 (2009): 16.

26. Sanders NL., *et al*. "Appendectomy and *Clostridium difficile* colitis: relationships revealed by clinical observations and immunology". *World Journal of Gastroenterology* 19.34 (2013): 5607-5614.

27. Potts JR 3rd. "What are the indications for cholecystectomy?" *Cleveland Clinic Journal of Medicine* 57.1 (1990): 40-47.

28. Nguyen A and Lotfollahzadeh S. "Appendectomy". National Library of Medicine. (NIH). National Center for biotechnology Information (2023).

29. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Treatment for appendicitis (2021).

30. Collard M., *et al*. "Antibiotics alone as an alternative to appendectomy for uncomplicated acute appendicitis in adults: Changes in treatment modalities related to the COVID-19 health crisis". *Journal of Visceral Surgery* 157.3S1 (2020): S33-S42.

31. Wang Q., *et al*. "Dysbiosis of gut microbiota after cholecystectomy is associated with non-alcoholic fatty liver disease in mice". *FEBS Open Bio* 11.8 (2021): 2329-2339.

32. Choi SJ., *et al*. "Association of microbial dysbiosis with gallbladder diseases identified by bile microbiome profiling". *Journal of Korean Medical Science* 36.28 (2021): e189.

33. Xu F., *et al*. "Cholecystectomy significantly alters gut microbiota homeostasis and metabolic profiles: a cross-sectional study". *Nutrients* 15.20 (2023): 4399.

34. Nakahara K., *et al*. "Gut microbiota of Parkinson's disease in an appendectomy cohort: a preliminary study". *Scientific Reports* 13.1 (2023): 2210.

35. Babakhanov AT., *et al*. "Impact of appendectomy on gut microbiota". *Surgical Infections (Larchmt)* 22.7 (2021): 651-661.

36. Maldonado Galdeano C., *et al*. "Stimulation of innate immune cells induced by probiotics: participation of toll-like receptors". *Journal of Clinical and Cellular Immunology* 6.1 (2015): 1000283.

37. Petruzziello C., *et al*. "Probiotics, the immune response and acute appendicitis: a review". *Vaccines (Basel)* 11.7 (2023): 1170.

38. Han ML., *et al*. "Probiotics for gallstone prevention in patients with bariatric surgery: A prospective randomized trial". *Asian Journal of Surgery* 45.12 (2022): 2664-2669.

39. J Liu., *et al*. "Acute cholecystitis associated with infection of Enterobacteriaceae from gut microbiota". *Clinical Microbiology and Infection* 21.9 (2015): 851.e1-851.e9.

40. Möller A., *et al*. "Changes in cytokine concentration during enrichment of early enteral nutrition with lactic acid bacterium (Synbiotic 2000) after major abdominal surgery". *Critical Care* 8.1 (2004): P273.

41. Yokoyama Y., *et al*. "Effects of synbiotics to prevent postoperative infectious complications in highly invasive abdominal surgery". *Annals of Nutrition and Metabolism* 71.1 (2017): 23-30.

42. Kim H., *et al*. "An unusual case of acute cholecystitis caused by *Lactobacillus paracasei*". *Cureus* 15.6 (2023): e40334.

43. Zhao JW., *et al*. "Fecal microbiota transplantation as potential first-line treatment for patients with *Clostridioides difficile* infection and prior appendectomy". *World Journal of Gastrointestinal Surgery* 15.2 (2023): 303-306.

44. Peery AF., *et al*. "AGA clinical practice guideline on fecal microbiota-based therapies for select gastrointestinal diseases". *Gastroenterology* 166.3 (2024): 409-434.

Volume 11 Issue 4 April 2024