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Chronic use of proton pump inhibitors and vitamin B12 deficiency: Current evidence and recommendations

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Iana Bantim Felício Calou
Doctor in Pharmacology
Associate Professor at the Federal University of Piauí

ABSTRACT
Proton pump inhibitors (PPIs) are among the most widely used drugs in the world. Representing the first choice of treatment for various disorders that affect the digestive system, these drugs are also among the most sought after for self-medication, since they are over-the-counter. The massive and prolonged use of PPIs ended up bringing to light adverse reactions that were eventually serious and often avoidable if they were used rationally. One of the main concerns about the chronic use of these drugs concerns their potential to cause vitamin B12 deficiency in chronic users, with damage ranging from megaloblastic anemia to severe neuropsychiatric disorders. Numerous studies have already addressed the topic without reaching a consensus. Currently, several indications postively relate the use of PPIs with vitamin B12 deficiency, and many others show the absence of a significant relationship. In general, the evidence is considered weak, and the recommendation among prescribers is that no action regarding serum monitoring or routine VB12 supplementation is necessary in patients on chronic use of proton pump inhibitors.

Keywords: Proton pump inhibitors, Vitamin B12, SIBO.

1 INTRODUCTION

Since the introduction of omeprazole to the pharmaceutical market in 1989, proton pump inhibitors (PPIs) have become the mainstay of the treatment of disorders related to gastric acidity, being among the most widely used medications in the world (Targownik et al., 2022). When confronted with previously used agents, such as histamine H2 receptor antagonists (H2RAs), synthetic prostaglandin analogues, and anticholinergics, PPIs demonstrate excellent patient tolerance, excellent safety, and more expressive suppression of gastric acid serrection (Strand et al, 2017), being the first choice for the treatment of esophagitis. non-erosive reflux disease, peptic ulcer disease, prevention of ulcers associated with non-steroidal anti-inflammatory drugs, Zollinger-Ellison syndrome, functional dyspepsia (Lassen, 2007), as well as an integral part of Helicobacter pylori eradication therapy (Hagiwara et al., 2015).

There is a growing perception of the indiscriminate use of PPIs worldwide, resulting from both medical overprescription and self-medication, since they are over-the-counter drugs (Kelly et al., 2015; Boardman et al., 2015). In the West, 25% of the population reports having heartburn at least once a month and 5% describe daily symptoms, explaining the high demand for these drugs (Paroni et al., 2016).

As PPIs have become more popular and more widely used, there has been an increase in the emergence of potentially adverse effects related to them (Elias; Targownik, 2019) with studies relating them to chronic kidney disease, bone fractures, pneumonia, dementia to, more recently, COVID-19, although the mechanisms and causalities of these relationships have not been pointed out (Targownik et al., 2022). Among these effects, the intestinal alterations evoked by the prolonged use of PPIs, such as mucosal damage and alteration of the microbiota, with consequent impact on nutrient absorption and the response of the immune barrier system and, finally, on the general health of the patient, have gained a lot of attention from researchers in recent years, however, research involving this theme presents conflicting and unclear results (Gómez-Escudero, 2023).

Several studies have positively linked the inhibition of gastric acid secretion with a higher frequency of small intestinal bacterial overgrowth syndrome (SIBO) (Fried et al., 1994; Thorens et al., 1996; Saettone et al., 2009; Zwolinska et al., 2013; Jacobs et al., 2013; Zhang et al., 2020). A study conducted with 200 PPI users observed that their risk of developing SIBO was up to eight times higher than among non-users, and that the severity of symptoms increased the longer the duration of treatment (Lombardo et al., 2010). A meta-analysis that related the use of PPIs and the occurrence of SIBO confirmed this association in aspirated colonies of the duodenum and ileum (Lo & Chan, 2013). These studies suggest that patients being treated with PPIs may have a high prevalence of digestive symptoms, especially of intestinal origin (Fujimori, 2015).

Contrary to this evidence, Weitsman et al. (2022), through microbiome sequencing and culture, stated that the use of PPIs does not cause hyperproliferation of Clostridium difficile or increase in the incidence of SIBO. However, in the analysis of the gut microbiome, users of IPBs showed higher abundances of the families Camphylobacteraceae and Bifidobacteriaceae and a lower number of Clostridiaceae families when compared to non-users, not observing any difference in the alpha and beta diversity of the duodenal microbiome nor significant differences in phylum, class or order level between individuals. A meta-analysis conducted in 2020, including 3192 patients, also found no association between PPIs and SIBO (Shah et al., 2020).

Although there is no consensus among researchers about the increased incidence of SIBO as a result of the chronic use of PPIs, it is possible to observe in all studies an alteration of the microbiota in the Small Intestine (DI), which can generate consequences with varying impacts on the user's health, depending on factors such as general health status, dose and duration of treatment. Significant alterations in the bacterial flora of the small intestine have a great impact on the nutritional status of the host once a competition for critical nutrients is established, in addition to causing changes in metabolism, damage to the absorptive mucosa and gastrointestinal symptoms that decrease the individual's food intake (Zaidel & Lin, 2003;

Even though the efficiency of digestion and absorption of nutrients is the responsibility of the intestine, it does not depend exclusively on it. The stomach plays an essential role in the assimilation of nutrients, so changes in its typical characteristics, such as acidity, possibly interfere with these absorption mechanisms (Losurdo et al., 2023). Several studies (Graziani et al., 1995; Saltzman et al., 1994) proved the importance of gastric acid secretion in the absorption of vitamins and minerals. The reduction of iron, making it more soluble and easily absorbed, is dependent on gastric acidity, and the stomach, in hypochlorhydria or achlorhydria induced by PPIs, may cause body iron depletion with consequent anemia. Achloridia also significantly decreases calcium absorption, since the ionization of its salts, an essential step for the absorption of the mineral, requires low pH (Dado et al., 2017).

Among the most impacted nutrients, both by the growth of anaerobic bacteria in the ID, which increases their use in addition to initiating a competition in the absorptive membrane (Quigley et al., 2020), and by the increase in gastric pH induced by PPIs, is vitamin B12 (VB12), also called cyanocobalamin. This vitamin depends on several factors for it to be absorbed. First, it must be released from the food matrix through peptic enzymes and low stomach pH, this same pH then favors the binding between vitamin B12 and Haptocorrine, preventing its hydrolysis by gastric acid and reducing its degradation by the intestinal microbiota. In the duodenum, vitamin B12 loses affinity for haptocorriin binding to intrinsic factor that aids in the absorption of B12 through the intestinal wall in the distal ileum by binding to Cubulin, the receptor of the B12-IF complex (Guéant et al., 2022). It is foreseeable, therefore, that a stomach in achloridia, resulting from the prolonged use of PPIs, will make it impossible to extract VB12 from the food matrix, with its availability for absorption in the ileum decreased (Damodharan et al., 2021). These theoretical aspects are reinforced by several population-based studies already conducted (Porter et al., 2021; Dries et al., 2022).

The first study to demonstrate reduced absorption of VB12 in response to the use of PPIs, in a dose-dependent manner, was conducted in healthy subjects who received omeprazole for two weeks. (Marcuard et al., 1994). After the publication of these data, several other studies were published corroborating their results. Termanini et al. (1998) demonstrated the increased risk of vitamin B12 deficiency due to long-term use of PPIs in a prospective study in patients with Zollinger-Ellison syndrome, indicating a 10.3-fold higher risk of vitamin B12 deficiency among users. A meta-analysis conducted in 2015 with 4 case-control studies and an observational study encompassing, in total, 4,254 cases and 19,228 controls, also found a positive association between chronic use of PPIs and the risk of developing vitamin B12 deficiency (Jung et al., 2015).

Lan et al (2013) in a case-control study comparing 25,956 patients with vitamin B12 deficiency with 184,199 patients without vitamin B12 deficiency found a positive association between PPI use and hypovitaminosis. Recently, a cohort study pointed out that the risk of developing VB12 deficiency is 50% higher among patients using PPIs, also showing a suggestive difference, through the t-test,

between the levels of the vitamin before and after treatment lasting two years (Mumtaz et al., 2022). Even the use of IPBs for relatively short periods of six months can cause clinical manifestations of vitamin B12 deficiency via oxidative stress, including neurotoxicity and cognitive decline (Dries et al., 2022).

The apparent irrefutable nature of the above data is not supported in practice and is contested by several studies. Starting with the fact that B12 hypovitaminosis is found in only 3.2% of adults in chronic PPI use (Evatt et al., 2010). A study of 200 patients found that 12 months of PPI use did not result in any changes in serum levels of cyanocobalamin and homocysteine (Qorraj-Bytyqi et al.,2018). Den Elzen et al. (2008) compared the serum levels of vitamin B12 and homocysteine in elderly individuals as well as the mean corpuscular volume between 125 PPI users for more than 3 years and 125 non-users, not finding any significant difference in the parameters between the groups.

Two studies that deserve to be highlighted (SOPRANO and LOTUS), because they encompass users of PPIs for long periods of time (5-12 years), had their data sitetized, and no significant difference in serum vitamin B12 levels was found between chronic and non-users of PPIs (Attwood et al., 2015). Reinforcing these results, a cross-sectional study including 25,953 individuals, analyzing the same parameters, also did not find any statistically significant difference between the groups, far from it, the researchers observed higher levels of vitamin B12 among users of IPBs, although this data did not show statistical significance (Lerman et al., 2022).

Basic differences between PPI users and non-users make it challenging to study potential adverse effects of these drugs retrospectively. For this reason, despite a large number of studies, the overall quality of the evidence for the adverse effects of PPIs ranges from low to very low. So many conflicting results of questionable validity, dealing with one of the most widely used classes of drugs in the world, has stimulated reviews and clinical recommendations carried out by experts aiming at the rational use of these agents in order to avoid, as much as possible, the emergence of adverse effects or even their inappropriate or unnecessary use (Freedberg et al., 2017).

Even though there is not enough evidence to recommend specific strategies to mitigate the adverse effects of PPIs, the American Gastroenterological Association has published clinical recommendations for good practices in the use of PPIs that have been recognized and implemented in various parts of the world (Ladera et al., 2020; SNS, 2017; Bhatia et al., 2019, AGRJ, 2022). The updates bring 10 recommendations, including the actions to be taken regarding the possible effects of these drugs on the small intestine and the absorption of VB12. Briefly, it is recommended: Patients in chronic use of PPIs should not take probiotics regularly in order to avoid infections (recommendation 7); Chronic users of PPIs should not routinely increase their intake of calcium, vitamin B12 or magnesium beyond the Recommended Daily Allowance (recommendation 8); Routine screening and monitoring of vitamin B12 levels in chronic users of PPIs (recommendation 9) is inappropriate

(Freedberg et al., 2017). In 2022, a new update was published, giving greater emphasis to the management of the deprescribing of this class of drugs (Targownik et al, 2022).

When IBs are prescribed appropriately, their benefits are likely to outweigh their risks. However, its inadequate prescription transforms modest risks into important ones, since there is no potential benefit (Vaezi et al., 2017). Despite the overwhelming number of studies linking the chronic use of proton pump inhibitors to vitamin B12 deficiency, the evidence is considered insufficient by competent medical committees that do not recommend routine vitamin B12 supplementation for PPI users.

Longer prospective studies, with careful monitoring of absorption and serum levels of VB12, are extremely necessary to resolve the questions surrounding the subject, clarifying whether possible serum changes occur and whether they are clinically relevant.

REFERENCES

AGRJ. Inibidores da bomba de prótons: 10 orientações sobre a suspensão do uso.17 JUN 2022. LINK:https://socgastro.org.br/novo/2022/06/inibidores-da-bomba-de-protons-10-orientacoes-sobre-a-suspensao-do-uso/

Attwood SE, Ell C, Galmiche JP, Fiocca R, Hatlebakk JG, Hasselgren B, Långström G, Jahreskog M, Eklund S, Lind T, Lundell L. Long-term safety of proton pump inhibitor therapy assessed under controlled, randomised clinical trial conditions: data from the SOPRAN and LOTUS studies. Aliment Pharmacol Ther. 2015 Jun;41(11):1162-74. doi: 10.1111/apt.13194. Epub 2015 Apr 10. PMID: 25858519.

Boardman HF, Delaney BC, Haag S. 2015. Partnership in optimizing management of reflux symptoms: a treatment algorithm for over-thecounter proton-pump inhibitors. Curr Med Res Opin 31:1309 –1318. http://dx.doi.org/10.1185/03007995.2015.1047745.

Bhatia S, Shukla A, Johnson D, Thatte U, Lawate P, Babu S, Rathi P, Khanna S, Sandeep MS, Rai V, Parchure N, Agrawal V. An Expert Review and Recommendations on the Rational Use of Proton Pump Inhibitors: Indian Perspective. J Assoc Physicians India. 2019 Apr;67(4):88-96. PMID: 31309811.

Cotter PE, O'Keeffe ST. Use of proton pump inhibitors is not associated with Vitamin B12 deficiency and in older hospital patients: A case control study, European Geriatric Medicine, Volume 2, Issue 4, 2011, Pages 253-255, ISSN 1878-7649, https://doi.org/10.1016/j.eurger.2011.02.007.

Dado DN, Loesch EB, Jaganathan SP. A Case of Severe Iron Deficiency Anemia Associated with Long-Term Proton Pump Inhibitor Use. Curr Ther Res Clin Exp. 2017 Jan 21;84:1-3. doi: 10.1016/j.curtheres.2017.01.003. PMID: 28761572; PMCID: PMC5522969.

Damodharan S, Raj GM, Sakthibalan M, Dakshinamoorthy K, Muraliswaran P. Effect of long-term acid suppression therapy with proton pump inhibitors or H_2 receptor blockers on serum vitamin B_{12} levels in elderly population. Ir J Med Sci. 2021 Aug;190(3):1213-1217. doi: 10.1007/s11845-020-02399-w. Epub 2020 Oct 21. PMID: 33085017.

Den Elzen, Wendy & Groeneveld, Y & de Ruijter, Wouter & Souverijn, J & Le Cessie, Saskia & Assendelft, Willem & Gussekloo, Jacobijn. (2008). Long-term use of proton pump inhibitors and vitamin B12 status in elderly individuals. Alimentary pharmacology & therapeutics. 27. 491-7. 10.1111/j.1365-2036.2008.03601.x.

Dries LS, Haefliger R, Seibert BS, de Lima AG, Cardoso CO, Perassolo MS. Cognition, oxidative stress and vitamin B12 levels evaluation on patients under long-term omeprazole use. J Pharm Pharmacol. 2022 Apr 20;74(4):547-555. doi: 10.1093/jpp/rgab001. PMID: 33793790.

Elias E, Targownik LE. The clinician's guide to proton pump inhibitor related adverse events. Drugs 2019; 79:715–731.

Evatt ML, Terry PD, Ziegler TR, Oakley GP. Association between vitamin B 12 -containing supplement consumption and prevalence of biochemically defined B 12 deficiency in adults in NHANES III (Third National Health and Nutrition Examination Survey). Public Health Nutr. 2010;13:25-31.

Freedberg DE, Kim LS, Yang YX. The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice From the American Gastroenterological

Association. Gastroenterology. 2017 Mar;152(4):706-715. doi: 10.1053/j.gastro.2017.01.031. PMID: 28257716.

Fried M, H. Siegrist, F. Froehlich, *et al*.Duodenal bacterial overgrowth during treatment in outpatients with omeprazole.Gut, 35 (1994), pp. 23-26

Fujimori,S. What are the effects of proton pump inhibitors on the small intestine?. World J Gastroenterol, 21 (2015), pp. 6817-6819.

Guéant JL, Guéant-Rodriguez RM, Alpers DH. Vitamin B12 absorption and malabsorption. Vitam Horm. 2022;119:241-274. doi: 10.1016/bs.vh.2022.01.016. Epub 2022 Mar 1. PMID: 35337622.

Gómez-Escudero O. Drug-Related Enteropathy [Internet]. Benign Anorectal Disorders - An Update. IntechOpen; 2023. Available from: http://dx.doi.org/10.5772/intechopen.103734

Graziani, G.; Como, G.; Badalamenti, S.; Finazzi, S.; Malesci, A.; Gallieni, M.; Brancaccio, D.; Ponticelli, C. Effect of gastric acid secretion on intestinal phosphate and calcium absorption in normal subjects. *Nephrol. Dial. Transplant.* 1995, *10*, 1376–1380.

Hagiwara T, Mukaisho K, Nakayama T, Hattori T, Sugihara H. Proton pump inhibitors and helicobacter pylori-associated pathogenesis. Asian Pac J Cancer Prev. 2015;16(4):1315-9. doi: 10.7314/apjcp.2015.16.4.1315. PMID: 25743791

Jacobs C, E. Coss Adame, A. Attaluri, *et al*. Dysmotility and proton pump inhibitor use are independent risk factors for small intestinal bacterial and/or fungal overgrowth. Aliment Pharmacol Ther, 37 (2013), pp. 1103-1111

Jung SB, Nagaraja V, Kapur A, Eslick GD. Association between vitamin B12 deficiency and long-term use of acid-lowering agents: a systematic review and meta-analysis. Intern Med J. 2015 Apr;45(4):409-16. doi: 10.1111/imj.12697. PMID: 25583062.

Kelly OB, Dillane C, Patchett SE, Harewood GC, Murray FE. 2015. The inappropriate prescription of oral proton pump inhibitors in the hospital setting: a prospective cross-sectional study. Dig Dis Sci 60:2280 –2286. http://dx.doi.org/10.1007/s10620-015-3642-8. 23.

Ladera, G.M. & Labari, M.E. & Pascual, J.N.. (2020). Actualización en la prescripción de inhibidores de la bomba de protones. Qué hacer y qué no hacer. Medicina de Familia. SEMERGEN. 47. 10.1016/j.semerg.2020.09.011.

Lam JR, Schneider JL, Zhao W, Corley DA. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency. JAMA. 2013 Dec 11;310(22):2435-42. doi: 10.1001/jama.2013.280490. PMID: 24327038.

Lassen AT. Acid-related disorders and use of antisecretory medication. Dan Med Bull. 2007;54:18–30
Lerman TT, Cohen E, Sochat T, Goldberg E, Goldberg I, Krause I. Proton pump inhibitor use and its effect on vitamin B12 and homocysteine levels among men and women: A large cross-sectional study. Am J Med Sci. 2022 Dec;364(6):746-751. doi: 10.1016/j.amjms.2022.07.006. Epub 2022 Jul 24.

Lo, WK, Chan WW.Proton pump inhibitor use and the risk of small intestinal bacterial overgrowth: A meta-analysis. Clin Gastroentero lHepatol, 11 (2013), pp. 483-490)

Lombardo L, Foti M, Ruggia O, Chiecchio A. Increased incidence of small intestinal bacterial overgrowth during proton pump inhibitor therapy. Clin Gastroenterol Hepatol. 2010 Jun;8(6):504-8. doi: 10.1016/j.cgh.2009.12.022. Epub 2010 Jan 6. PMID: 20060064.

Losurdo, G.; Caccavo, N.L.B.; Indellicati, G.; Celiberto, F.; Ierardi, E.; Barone, M.; Di Leo, A. Effect of Long-Term Proton Pump Inhibitor Use on Blood Vitamins and Minerals: A Primary Care Setting Study. *J. Clin. Med.* 2023, *12*, 2910. https://doi.org/10.3390/jcm12082910.

Marcuard S.P., Albernaz L., Khazanie P.G. Omeprazole therapy causes malabsorption of cyanocobalamin (vitamin B12) *Ann. Intern. Med.* 1994;120:211–215. doi: 10.7326/0003-4819-120-3-199402010-00006.

Mumtaz H, Ghafoor B, Saghir H, Tariq M, Dahar K, Ali SH, Waheed ST, Syed AA. Association of Vitamin B12 deficiency with long-term PPIs use: A cohort study. Ann Med Surg (Lond). 2022 Sep 26;82:104762. doi: 10.1016/j.amsu.2022.104762. PMID: 36268318; PMCID: PMC9577826.

Paroni Sterbini F, Palladini A, Masucci L, Cannistraci CV, Pastorino R, Ianiro G, Bugli F, Martini C, Ricciardi W, Gasbarrini A, Sanguinetti M, Cammarota G, Posteraro B. Effects of Proton Pump Inhibitors on the Gastric Mucosa-Associated Microbiota in Dyspeptic Patients. Appl Environ Microbiol. 2016 Oct 27;82(22):6633-6644. doi: 10.1128/AEM.01437-16. PMID: 27590821; PMCID: PMC5086557.

Porter K.M., Hoey L., Hughes C.F., et al. Associations of atrophic gastritis and proton-pump inhibitor drug use with vitamin B-12 status, and the impact of fortified foods, in older adults. *Am. J. Clin. Nutr.* 2021 Oct 4;114(4):1286–1294. doi: 10.1093/ajcn/nqab193. PMID: 34134144; PMCID: PMC8488868.

Qorraj-Bytyqi H, Hoxha R, Sadiku S, Bajraktari IH, Sopjani M, Thaçi K, Thaçi S, Bahtiri E. Proton Pump Inhibitors Intake and Iron and Vitamin B12 Status: A Prospective Comparative Study with a Follow up of 12 Months. Open Access Maced J Med Sci. 2018 Mar 12;6(3):442-446. doi: 10.3889/oamjms.

Quigley E.M., Murray J.A., Pimentel M. AGA Clinical Practice Update on Small Intestinal Bacterial Overgrowth: Expert Review. *Gastroenterology.* 2020;159:1526–1532. doi: 10.1053/j.gastro.2020.06.090a.22

Saettone S, L. Broglia, P. Occhipinti. Prevalence of small bowel intestinal bacterial overgrowth (SIBO) in chronic proton pump inhibitors users: A pilot case-control study. Dig Liver Dis, 41 (2009), pp. S142 Saltzman, J.R.; Kemp, J.A.; Golner, B.B.; Pedrosa, M.C.; Dallal, G.E.; Russell, R.M. Effect of hypochlorhydria due to omeprazole treatment or atrophic gastritis on protein-bound vitamin B12 absorption. *J. Am. Coll. Nutr.* 1994, *13*, 584–591.

Shah A, Talley NJ, Jones M, Kendall BJ, Koloski N, Walker MM, Morrison M, Holtmann GJ. Small Intestinal Bacterial Overgrowth in Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis of Case-Control Studies. Am J Gastroenterol. 2020 Feb;115(2):190-201. doi: 10.14309/ajg.0000000000000504. PMID: 31913194.

SNS.Boletim/Recomendação Da CFT. Inibidores de bomba de prótons N 3, 2019.

Strand DS, Kim D, Peura DA. 25 Years of Proton Pump Inhibitors: A Comprehensive Review. Gut Liver. 2017 Jan 15;11(1):27-37. doi: 10.5009/gnl15502. PMID: 27840364; PMCID: PMC5221858.

Targownik LE, Fisher DA, Saini SD. AGA Clinical Practice Update on De-Prescribing of Proton Pump Inhibitors: Expert Review. Gastroenterology. 2022 Apr;162(4):1334-1342. doi: 10.1053/j.gastro.2021.12.247. Epub 2022 Feb 17. PMID: 35183361.

Termanini B., Gibril F., Sutliff V.E., Yu F., Venzon D.J., Jensen R.T. Effect of long-term gastric acid suppressive therapy on serum vitamin B12 levels in patients with Zollinger-Ellison syndrome. *Am. J. Med.* 1998;104:422. doi: 10.1016/S0002-9343(98)00087.

Thorens S, F. Froehlich, W. Schwizer, *et al*. Bacterial overgrowth during treatment with omeprazole compared with cimetidine: A prospective randomized double blind study. Gut, 39 (1996), pp. 54-59.
Vaezi MF, Yang YX, Howden CW. Complications of proton pump inhibitor therapy. Gastroenterology 2017; 153:35–48.

Weitsman S, Celly S, Leite G, Mathur R, Sedighi R, Barlow GM, Morales W, Sanchez M, Parodi G, Villanueva-Millan MJ, Rezaie A, Pimentel M. Effects of Proton Pump Inhibitors on the Small Bowel and Stool Microbiomes. Dig Dis Sci. 2022 Jan;67(1):224-232. doi: 10.1007/s10620-021-06857-y. Epub 2021 Feb 3. PMID: 33534012.

Zaidel O, and Lin HC. Uninvited Guests: The Impact of Small Intestinal Bacterial Overgrowth on Nutritional Status. NUTRITION ISSUES IN GASTROENTEROLOGY, SERIES #7. PRACTICAL GASTROENTEROLOGY • JULY 2003

Zhang R, Li Y, Ma JX, Tang S, Li CM, Wan J. [The effects of continuous proton pump inhibitor therapy on small intestinal bacterial overgrowth in elderly]. Zhonghua Nei Ke Za Zhi. 2020 Sep 1;59(9):706-710. Chinese. doi: 10.3760/cma.j.cn112138-20191218-00823. PMID: 32838502.

Zwolinska M Wcislo, M. Przybylska Felus, A. Piateck Guziewicz, *et al*. Small Intestinal bacterial overgrowth and gastrointestinal symptoms in celiac disease patients receiving proton pump inhibitors. UEG Journal, 1 (2013), pp. A579