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主编

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传真: 010-85381893

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Editorial Board Member of *World Chinese Journal of Digestology*, De liang Liu, Professor, Chief Physician, Department of Gastroenterology, The Second Xiangya Hospital of Central South University, No.139 Renmin Middle Road, Furong District, Changsha 410011, Hunan Province, China

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7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA

Fax: +1-925-223-8242

Telephone: +1-925-223-8243

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PPIs使用与NSAIDs相关小肠损伤: 如何平衡风险和获益

朱兰平, 赵经文, 陈鑫, 王邦茂

朱兰平, 赵经文, 陈鑫, 王邦茂, 天津医科大学总医院消化内科 天津市 300052

陈鑫, 副主任医师, 主要从事消化系早癌诊治与基础相关研究.

作者贡献分布: 本述评由朱兰平与赵经文撰写; 陈鑫与王邦茂审校.

通讯作者: 陈鑫, 副教授, 副主任医师, 300052, 天津市和平区鞍山道154号, 天津医科大学总医院消化内科. xchen03@tmu.edu.cn
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Proton pump inhibitor usage and nonsteroidal anti-inflammatory drugs-associated small intestinal injury: How to balance risks and benefits

Lan-Ping Zhu, Jing-Wen Zhao, Xin Chen, Bang-Mao Wang

Lan-Ping Zhu, Jing-Wen Zhao, Xin Chen, Bang-Mao Wang, Department of Gastroenterology and Hepatology, General Hospital of Tianjin Medical University, Tianjin 300052, China

Correspondence to: Xin Chen, Associate Professor, Associate Chief Physician, Department of Gastroenterology and Hepatology, General Hospital of Tianjin Medical University, 154 Anshan Road, Heping District, Tianjin 300052, China. xchen03@tmu.edu.cn

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Abstract

Proton pump inhibitors (PPIs) are widely used in the treatment of acid-related diseases and can effectively

prevent upper gastrointestinal damage associated with nonsteroidal anti-inflammatory drugs (NSAIDs). However, recent studies have shown that PPIs cannot protect from NSAIDs-associated small bowel injury, and may even aggravate intestinal injury by altering the intestinal flora. This article will discuss the risks associated with the combined use of NSAIDs and PPIs, as well as how to balance risks and benefits of PPIs treatment, and provide a brief review of strategies for the prevention of NSAIDs-associated small bowel injury.

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Key Words: Proton pump inhibitors; Nonsteroidal anti-inflammatory drugs; Small intestinal injury; Risks and benefits

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摘要

质子泵抑制剂(proton pump inhibitors, PPIs)被广泛应用于酸相关疾病的治疗,能有效防治非甾体抗炎药(nonsteroidal anti-inflammatory drugs, NSAIDs)相关的上消化道损伤.但是,最近的研究表明,PPIs无法防治NSAIDs相关小肠损伤,甚至可能通过改变肠道菌群加重小肠损伤.本文将讨论NSAIDs和PPIs联合用药的风险,以及如何平衡PPIs使用的风险和获益,并对NSAIDs相关小肠损伤的防治策略做一简单综述.

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关键词: 质子泵抑制剂; 非甾体抗炎药; 小肠损伤; 风险和获益

核心提要: 质子泵抑制剂(proton pump inhibitors, PPIs)可降低上消化道损伤风险, 却通过改变肠道菌群加重非甾体抗炎药相关小肠损伤。未来的研究需充分评估风险和获益, 减少不当的PPIs使用, 以及进一步评估可能的药物干预效果, 以降低消化道损伤的风险。

朱兰平, 赵经文, 陈鑫, 王邦茂. PPIs使用与NSAIDs相关小肠损伤: 如何平衡风险和获益. 世界华人消化杂志 2018; 26(22): 1334-1339 URL: <http://www.wjgnet.com/1009-3079/full/v26/i22/1334.htm> DOI: <http://dx.doi.org/10.11569/wcjd.v26.i22.1334>

0 引言

非甾体抗炎药(nonsteroidal anti-inflammatory drugs, NSAIDs)是临床上广泛使用的解热、镇痛和抗炎药物。近年来, 由于阿司匹林广泛应用于心脑血管疾病的预防, 并已初步证实可降低结直肠癌的发病率^[1,2], 因而NSAIDs的应用呈现上升趋势。但NSAIDs长期使用时副作用较多, 其中最常见的是胃肠黏膜损伤。既往我们只注意到胃、十二指肠黏膜的损伤, 但近年来随着胶囊内镜和小肠镜的开展, 发现NSAIDs还可引起小肠黏膜损伤, 包括红斑、糜烂、溃疡、出血和隔膜样狭窄等^[3,4]。Graham等^[5]对NSAIDs长期服用者行胶囊内镜检查, 发现71%的患者发生了小肠损伤; Endo等^[6]发现健康受试者在使用低剂量NSAIDs 2 wk后, 小肠损伤的发生率为80%。由此可见NSAIDs相关小肠损伤的发生率很高, 甚至高于上消化道损伤的发生率^[7,8]。

质子泵抑制剂(proton pump inhibitors, PPIs)自面世以来, 因其良好的抑酸功能, 被广泛应用于胃食管反流病、消化性溃疡和消化道出血等酸相关疾病的治疗。PPIs能有效防治NSAIDs相关的上消化道损伤, 因此, 在临床实践中NSAIDs和PPIs联用一直被认为是安全有效的^[9]。然而, 最近更多的证据表明, PPIs的抑酸作用不但不能对位于更远端的小肠有任何保护作用, 甚至加重NSAIDs相关小肠损伤^[10]。本文对NSAIDs和PPIs联合用药的风险及如何平衡PPIs使用的风险和获益做一述评。

1 PPIs使用与NSAIDs相关小肠损伤的风险

一项病例对照研究纳入了978例因消化道出血而住院的患者, 服用NSAIDs、抗血小板药或抗凝药增加了上、下消化道出血的风险, 而PPIs的使用只降低了上消化道出血的风险^[11]。Arroyo等^[12]发现, 在联合使用PPIs和双重抗血小板药物的患者中, 下消化道出血的发生率较上消化道更高(74% vs 26%)。一项多中心横断面研究收集了

205例患者的胶囊内镜检查数据, 发现57.6%的患者在服用低剂量阿司匹林3 mo后出现了小肠黏膜损伤。多元分析结果显示, 合用PPIs(OR = 2.04; 95%CI: 1.05-3.97)是小肠黏膜损伤的独立危险因素^[13]。在最近的一项随机安慰剂对照试验中, 57名健康志愿者被随机分成两组, 2 wk后塞来昔布+雷贝拉唑组小肠黏膜损伤的发生率明显高于塞来昔布+安慰剂组(44.7% vs 16.7%, $P = 0.04$)^[14]。以上研究表明, PPIs不仅不能保护使用NSAIDs患者的小肠黏膜, 而且可能加重黏膜损伤。

PPIs加重NSAIDs相关小肠损伤或与肠道菌群失调有关。PPIs抑酸作用强, 胃液pH值上升, 对细菌的杀灭作用减弱, 可使上消化道内细菌异位, 引起小肠菌群失调。Wallace等^[15]通过动物实验发现: PPIs与NSAIDs合用后明显加重了大鼠小肠黏膜损伤; 单独给PPIs使空肠内放线菌门和双歧杆菌减少, 而重新定植富含双歧杆菌的共生菌可减轻PPIs与NSAIDs联用所致的小肠损伤; 另外, 无菌小鼠移植PPIs处理的大鼠肠内容物后加重了NSAIDs相关小肠损伤。亦有证据显示, 联用PPIs加重小肠损伤可能与肠道菌群及胆汁酸的共同作用有关。动物实验发现, 长期使用PPIs增加了胆汁酸的细胞毒性, 加重了NSAIDs相关小肠损伤。由于PPIs改变肠道菌群, 增加了能将初级胆汁酸转化为次级胆汁酸的细菌数量, 使肠道内的次级胆汁酸浓度升高, 而次级胆汁酸的细胞毒性更强, 从而加重了小肠损伤^[16]。

近年来, 因下消化道出血的患者住院率显著增加^[17,18]。老年人群通常合并其他疾病, 所以更容易发生下消化道出血, 往往住院时间更长, 死亡率更高^[17]。由于缺乏统一的管理规范, 部分患者出院后停用阿司匹林或抗凝药物, 增加了严重心血管事件发生的风险^[19]。近期一项回顾性研究纳入了295例被诊断过下消化道出血的患者, 发现停用低剂量阿司匹林后, 下消化道出血的再发风险(6.9% vs 18.9%, $P = 0.007$)降低, 但是死亡率(26.7% vs 8.2%, $P = 0.001$)和心血管事件发生率(36.5% vs 22.8%, $P = 0.017$)增加^[20]。因此, 对于需长期服用NSAIDs患者, 平衡风险和获益是难点也是重点。

2 平衡PPIs使用的风险和获益

PPIs能有效防治NSAIDs相关的上消化道损伤, 却可能加重NSAIDs相关小肠损伤。面对这一临床困境, 我们需充分平衡风险和获益。一方面, 遵循适应证, 合理应用PPI; 另一方面, 必要时选择对消化道损伤相对较小的选择性环氧合酶2(COX-2)抑制剂; 此外, 积极寻求NSAIDs相关小肠损伤的药物防治新策略。

2.1 合理使用PPIs 在日常的临床实践中, PPIs常被过度使用, 至少50%的处方是没有合理适应症的^[21]。针对

NSAIDs使用者的PPIs应用, 应充分评估胃肠道损伤风险. 对于低风险患者, 应避免使用PPIs, 因为使用PPIs后不但起不到保护作用, 反而加重NSAIDs相关小肠损伤. 但是对于长期使用NSAIDs、有较高出血风险的患者, 不应停用PPIs. 消化道出血患者出院后, 我们应长期监测、评估患者病情, 以便及时调整PPIs剂量和持续用药时间^[22]. 在欧洲的一项对初级保健医师的调查中发现, 仅一半医生常规检测骨关节炎患者的血红蛋白浓度^[23]. 虽然预防消化道损伤很重要, 但定期监测仍然有必要, 有利于尽早发现损伤并进行治疗, 也可防止并发症的发生^[24]. 此外, 我们必须重新考虑目前指南的可靠性. PPIs防治NSAIDs相关胃肠损伤的指征是基于长期NSAIDs使用者的临床试验数据确定的^[25]. 然而, 观察性研究表明, 消化道出血的风险可能在NSAIDs短期使用者中更高, 而且大多数患者短期服用这些药物^[26].

2.2 改用选择性COX-2抑制剂 对于长期使用NSAIDs患者, 最新共识建议低出血风险患者使用非选择性NSAIDs, 而高出血风险患者使用选择性COX-2抑制剂^[27]. 因此, 如果患者在长期服用非选择性NSAIDs过程中出现了消化道损伤, 可以改用选择性COX-2抑制剂, 并积极治疗损伤^[3]. 一项Meta分析发现, 与非选择性NSAIDs相比, 选择性COX-2抑制剂和PPIs联用可显著降低消化道穿孔、梗阻和出血风险^[28]. 此外, 非选择性NSAIDs是亲脂弱酸, 能破坏疏水屏障, 直接损伤磷脂细胞膜, 导致小肠黏膜通透性增加^[29]. 使用酸性更弱的选择性COX-2抑制剂可能降低小肠损伤的风险^[24].

2.3 防治NSAIDs相关小肠损伤 目前尚无明确有效的药物防治NSAIDs相关小肠损伤. 一些研究评估了黏膜保护剂、益生菌等药物的防治效果.

2.3.1 黏膜保护剂: 米索前列醇是一种前列腺素类似物, 能通过刺激黏液/碳酸氢盐分泌和增强肠屏障功能, 发挥黏膜保护作用. 研究显示, 米索前列醇可改善NSAIDs破坏的肠道通透性, 有效治疗低剂量肠溶阿司匹林和双氯芬酸所致的肠病^[30,31]. 但其副作用如腹泻和腹痛发生率高, 患者的耐受性差, 所以在临床上使用受限^[32].

瑞巴派特和替普瑞酮能促进黏液分泌, 刺激内源性前列腺素生成, 清除氧自由基, 是临床上常用的胃黏膜保护剂. Niwa等^[33]进行了一项前瞻性双盲安慰剂对照研究, 让健康受试者服用瑞巴派特/安慰剂和双氯芬酸7 d, 发现瑞巴派特能明显减轻NSAIDs相关小肠损伤(20% vs 80%, $P<0.05$). 另一项前瞻性双盲研究表明, 替普瑞酮能保护双氯芬酸引起的胃和小肠损伤^[34]. Iwai等^[35]通过动物实验发现, 替普瑞酮可能通过增强小肠黏膜屏障、抑制细菌入侵来防治NSAIDs相关小肠损伤.

2.3.2 抗生素: 菌群失衡参与了NSAIDs相关小肠损伤的发生, 无菌鼠或多种抗生素处理的小鼠服用NSAIDs不会出现小肠损伤^[36-38], 所以抗生素对NSAIDs相关小肠损伤有防治作用^[39]. Davies等^[40]给9位使用NSAIDs的健康受试者服用甲硝唑后, 明显改善了小肠黏膜的通透性. 另一项安慰剂对照研究中, 健康受试者同时服用利福昔明和双氯芬酸2 wk后, 小肠黏膜损伤的发生率明显低于对照组(20% vs 43%), 且对照组有9人出现了较大的黏膜损伤, 而利福昔明组未出现^[41]. 尽管多项研究证实抗生素有效, 但考虑到其潜在的副作用和细菌的耐药, 抗生素的长期联合使用在临床上并不现实.

2.3.3 益生菌: 动物实验发现, 某些益生菌(干酪乳杆菌、双歧杆菌等)能明显减轻大鼠NSAIDs相关小肠损伤^[42,43]. Montalto等^[44]进行了一项随机双盲安慰剂对照实验, 所有健康受试者服用吡哆美辛4 d, 实验组同时服用益生菌制剂VSL#3(含8种不同活菌), 粪便钙卫蛋白的检测水平作为评价小肠损伤的指标. 服药期间安慰剂对照组粪便钙卫蛋白水平明显升高, 而益生菌组始终维持在正常水平. 另一项临床研究中, 25例服用低剂量肠溶阿司匹林和奥美拉唑超过3 mo出现不明原因缺铁性贫血的患者, 服用干酪乳杆菌或安慰剂治疗3 mo后, 胶囊内镜检查发现服用益生菌组患者小肠黏膜损伤评分明显低于安慰剂组^[45]. 近期的一项随机安慰剂对照交叉试验发现, NSAID降低了健康受试者血中CD4+/Foxp3 Treg细胞数量, 但可被植物乳杆菌菌株TIFN101抑制; 另外此菌株可上调小肠黏膜中维持T、B细胞功能及抗原呈递相关基因的表达, 表明益生菌可提高人体黏膜和全身的免疫功能, 抑制NSAID引起的Treg细胞减少^[46].

2.3.4 NSAIDs衍生物: 内源性NO和H₂S能扩张血管、修复肠黏膜及抑制白细胞黏附, 对维持胃肠道黏膜完整性具有重要作用^[47,48]. 开发可释放NO或H₂S的NSAIDs衍生物能保护NSAIDs对小肠黏膜的损伤. 研究显示, NO-NSAID明显减轻小肠黏膜损伤, 实验动物亦有较好的耐受性^[49,50]. 在一项小样本的短期临床试验中, NO-NSAID对小肠通透性的影响明显小于NSAID本身^[51]. 亦有研究证实, H₂S-NSAID可通过降低胆汁的细胞毒性和调节肠道菌群减轻小肠黏膜损伤^[16,52].

2.3.5 新型组胺H2受体拮抗剂: 拉呋替丁是一种具有抑酸和消化道黏膜保护作用的特殊组胺H2受体拮抗药, 抑酸作用强而持久, 可激活辣椒素敏感传入神经, 介导降钙素基因相关肽、生长抑素和一氧化氮释放, 增加胃黏膜血流量, 促进黏膜上皮再生, 刺激黏液分泌, 进而保护消化道黏膜(胃黏膜, 肠黏膜, 食管黏膜), 抵御攻击因子(胃酸、胆汁、酒精、NSAIDs、化疗药物等)对黏膜的损伤, 并促进溃疡愈合, 防止溃疡复发^[53-57]. 拉呋替丁

既能抑制胃酸分泌保护胃黏膜, 又可通过激活辣椒素敏感传入神经, 防治NSAIDs相关小肠损伤, 有望成为理想的“NSAIDs伴侣”, 但仍需进一步的临床实验验证。

3 结论

PPIs可有效防治NSAIDs相关上消化道损伤, 却加重NSAIDs相关小肠损伤。因此在临床实践中需充分评估风险和获益, 合理应用PPIs来防治NSAIDs相关胃肠黏膜损伤。此外, 对于高出血风险患者, 改用选择性COX-2抑制剂, 可降低小肠损伤的风险。未来的研究需进一步评估黏膜保护剂、益生菌、NSAIDs衍生物和新型组胺H2受体拮抗剂等防治NSAIDs相关小肠损伤药物的效果。

4 参考文献

- Bosetti C, Rosato V, Gallus S, Cuzick J, La Vecchia C. Aspirin and cancer risk: a quantitative review to 2011. *Ann Oncol* 2012; 23: 1403-1415 [PMID: 22517822 DOI: 10.1093/annonc/mds113]
- Fletcher RH. Review: Aspirin reduces colorectal cancer incidence and mortality in patients at average risk. *Ann Intern Med* 2016; 165: JC16 [PMID: 27538177 DOI: 10.7326/ACPJC-2016-165-4-016]
- Tacheci I, Bradna P, Douda T, Baštecká D, Kopáčová M, Rejchrt S, Bureš J. NSAID-Induced Enteropathy in Rheumatoid Arthritis Patients with Chronic Occult Gastrointestinal Bleeding: A Prospective Capsule Endoscopy Study. *Gastroenterol Res Pract* 2013; 2013: 268382 [PMID: 24382953 DOI: 10.1155/2013/268382]
- Ullah S, Ajab S, Rao R, Raghunathan G, DaCosta P. Diaphragm disease of the small intestine: an interesting case report. *Int J Surg Pathol* 2015; 23: 322-324 [PMID: 25525150 DOI: 10.1177/1066896914563392]
- Graham DY, Opekun AR, Willingham FF, Qureshi WA. Visible small-intestinal mucosal injury in chronic NSAID users. *Clin Gastroenterol Hepatol* 2005; 3: 55-59 [PMID: 15645405]
- Endo H, Hosono K, Inamori M, Kato S, Nozaki Y, Yoneda K, Akiyama T, Fujita K, Takahashi H, Yoneda M, Abe Y, Kirikoshi H, Kobayashi N, Kubota K, Saito S, Matsuhashi N, Nakajima A. Incidence of small bowel injury induced by low-dose aspirin: a crossover study using capsule endoscopy in healthy volunteers. *Digestion* 2009; 79: 44-51 [PMID: 19246922 DOI: 10.1159/000204465]
- Adebayo D, Bjarnason I. Is non-steroidal anti-inflammatory drug (NSAID) enteropathy clinically more important than NSAID gastropathy? *Postgrad Med J* 2006; 82: 186-191 [PMID: 16517800 DOI: 10.1136/pgmj.2005.039586]
- McCarthy DM. GI bleeding: problems that persist. *Gastrointest Endosc* 2009; 70: 225-228 [PMID: 19631801 DOI: 10.1016/j.gie.2008.12.247]
- Lau JY, Barkun A, Fan DM, Kuipers EJ, Yang YS, Chan FK. Challenges in the management of acute peptic ulcer bleeding. *Lancet* 2013; 381: 2033-2043 [PMID: 23746903 DOI: 10.1016/S0140-6736(13)60596-6]
- Daniell HW. NSAID-PPI enteropathy in humans. *Gastroenterology* 2012; 142: e20; author reply e20-e20; author reply e21 [PMID: 22374457 DOI: 10.1053/j.gastro.2012.02.004]
- Lanas A, Carrera-Lasfuentes P, Arguedas Y, García S, Bujanda L, Calvet X, Ponce J, Perez-Aisa A, Castro M, Muñoz M, Sostres C, García-Rodríguez LA. Risk of upper and lower gastrointestinal bleeding in patients taking nonsteroidal anti-inflammatory drugs, antiplatelet agents, or anticoagulants. *Clin Gastroenterol Hepatol* 2015; 13: 906-912 [PMID: 25460554 DOI: 10.1016/j.cgh.2014.11.007]
- Casado Arroyo R, Polo-Tomas M, Roncalés MP, Scheiman J, Lanas A. Lower GI bleeding is more common than upper among patients on dual antiplatelet therapy: long-term follow-up of a cohort of patients commonly using PPI co-therapy. *Heart* 2012; 98: 718-723 [PMID: 22523056 DOI: 10.1136/heartjnl-2012-301632]
- Endo H, Sakai E, Taniguchi L, Kessoku T, Komiya Y, Ezuka A, Kawamura H, Taguri M, Higurashi T, Ohkubo H, Yamada E, Takahashi H, Inamori M, Maeda S, Sakaguchi T, Hata Y, Nagase H, Nakajima A. Risk factors for small-bowel mucosal breaks in chronic low-dose aspirin users: data from a prospective multicenter capsule endoscopy registry. *Gastrointest Endosc* 2014; 80: 826-834 [PMID: 24830581 DOI: 10.1016/j.gie.2014.03.024]
- Washio E, Esaki M, Maehata Y, Miyazaki M, Kobayashi H, Ishikawa H, Kitazono T, Matsumoto T. Proton Pump Inhibitors Increase Incidence of Nonsteroidal Anti-Inflammatory Drug-Induced Small Bowel Injury: A Randomized, Placebo-Controlled Trial. *Clin Gastroenterol Hepatol* 2016; 14: 809-815.e1 [PMID: 26538205 DOI: 10.1016/j.cgh.2015.10.022]
- Wallace JL, Syer S, Denou E, de Palma G, Vong L, McKnight W, Jury J, Bolla M, Bercik P, Collins SM, Verdu E, Ongini E. Proton pump inhibitors exacerbate NSAID-induced small intestinal injury by inducing dysbiosis. *Gastroenterology* 2011; 141: 1314-1322, 1322.e1-1322.e5 [PMID: 21745447 DOI: 10.1053/j.gastro.2011.06.075]
- Blackler RW, De Palma G, Manko A, Da Silva GJ, Flannigan KL, Bercik P, Surette MG, Buret AG, Wallace JL. Deciphering the pathogenesis of NSAID enteropathy using proton pump inhibitors and a hydrogen sulfide-releasing NSAID. *Am J Physiol Gastrointest Liver Physiol* 2015; 308: G994-1003 [PMID: 25882612 DOI: 10.1152/ajpgi.00066.2015]
- Lanas A, García-Rodríguez LA, Polo-Tomás M, Ponce M, Alonso-Abreu I, Perez-Aisa MA, Perez-Gisbert J, Bujanda L, Castro M, Muñoz M, Rodrigo L, Calvet X, Del-Pino D, Garcia S. Time trends and impact of upper and lower gastrointestinal bleeding and perforation in clinical practice. *Am J Gastroenterol* 2009; 104: 1633-1641 [PMID: 19574968 DOI: 10.1038/ajg.2009.164]
- Lanas A, García-Rodríguez LA, Polo-Tomás M, Ponce M, Quintero E, Perez-Aisa MA, Gisbert JP, Bujanda L, Castro M, Muñoz M, Del-Pino MD, Garcia S, Calvet X. The changing face of hospitalisation due to gastrointestinal bleeding and perforation. *Aliment Pharmacol Ther* 2011; 33: 585-591 [PMID: 21205256 DOI: 10.1111/j.1365-2036.2010.04563.x]
- Sostres C, Lanas A. Epidemiology of Low Dose Aspirin Damage in the Lower Gastrointestinal Tract. *Curr Pharm Des* 2015; 21: 5094-5100 [PMID: 26369682]
- Chan FK, Leung Ki EL, Wong GL, Ching JY, Tse YK, Au KW, Wu JC, Ng SC. Risks of Bleeding Recurrence and Cardiovascular Events With Continued Aspirin Use After Lower Gastrointestinal Hemorrhage. *Gastroenterology* 2016; 151: 271-277 [PMID: 27130815 DOI: 10.1053/j.gastro.2016.04.013]
- Lanas A. We Are Using Too Many PPIs, and We Need to Stop: A European Perspective. *Am J Gastroenterol* 2016; 111: 1085-1086 [PMID: 27166129 DOI: 10.1038/ajg.2016.166]
- Savarino V, Dulbecco P, de Bortoli N, Ottonello A, Savarino E. The appropriate use of proton pump inhibitors (PPIs): Need for a reappraisal. *Eur J Intern Med* 2017; 37: 19-24 [PMID: 27166129 DOI: 10.1038/ajg.2016.166]

- 27784575 DOI: 10.1016/j.jejim.2016.10.007]
- 23 Walker C, Faustino A, Lanas A. Monitoring complete blood counts and haemoglobin levels in osteoarthritis patients: results from a European survey investigating primary care physician behaviours and understanding. *Open Rheumatol J* 2014; 8: 110-115 [PMID: 25598854 DOI: 10.2174/187431290]
- 24 Gwee KA, Goh V, Lima G, Setia S. Coprescribing proton-pump inhibitors with nonsteroidal anti-inflammatory drugs: risks versus benefits. *J Pain Res* 2018; 11: 361-374 [PMID: 29491719 DOI: 10.2147/JPR.S156938]
- 25 Lué A, Lanas A. Protons pump inhibitor treatment and lower gastrointestinal bleeding: Balancing risks and benefits. *World J Gastroenterol* 2016; 22: 10477-10481 [PMID: 28082800 DOI: 10.3748/wjg.v22.i48.10477]
- 26 Lanas A, García-Rodríguez LA, Arroyo MT, Gomollón F, Feu F, González-Pérez A, Zapata E, Bástida G, Rodrigo L, Santolaria S, Güell M, de Argila CM, Quintero E, Borda F, Piqué JM; Asociación Española de Gastroenterología. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. *Gut* 2006; 55: 1731-1738 [PMID: 16687434 DOI: 10.1136/gut.2005.080754]
- 27 Scarpignato C, Lanas A, Blandizzi C, Lems WF, Hermann M, Hunt RH; International NSAID Consensus Group. Safe prescribing of non-steroidal anti-inflammatory drugs in patients with osteoarthritis—an expert consensus addressing benefits as well as gastrointestinal and cardiovascular risks. *BMC Med* 2015; 13: 55 [PMID: 25857826 DOI: 10.1186/s12916-015-0285-8]
- 28 Jarupongprapa S, Ussavasodhi P, Katchamart W. Comparison of gastrointestinal adverse effects between cyclooxygenase-2 inhibitors and non-selective, non-steroidal anti-inflammatory drugs plus proton pump inhibitors: a systematic review and meta-analysis. *J Gastroenterol* 2013; 48: 830-838 [PMID: 23208017 DOI: 10.1007/s00535-012-0717-6]
- 29 Bjarnason I, Takeuchi K. Intestinal permeability in the pathogenesis of NSAID-induced enteropathy. *J Gastroenterol* 2009; 44 Suppl 19: 23-29 [PMID: 19148789 DOI: 10.1007/s00535-008-2266-6]
- 30 Watanabe T, Sugimori S, Kameda N, Machida H, Okazaki H, Tanigawa T, Watanabe K, Tominaga K, Fujiwara Y, Oshitani N, Higuchi K, Arakawa T. Small bowel injury by low-dose enteric-coated aspirin and treatment with misoprostol: a pilot study. *Clin Gastroenterol Hepatol* 2008; 6: 1279-1282 [PMID: 18995219 DOI: 10.1016/j.cgh.2008.06.021]
- 31 Fujimori S, Seo T, Gudis K, Ehara A, Kobayashi T, Mitsui K, Yonezawa M, Tanaka S, Tatsuguchi A, Sakamoto C. Prevention of nonsteroidal anti-inflammatory drug-induced small-intestinal injury by prostaglandin: a pilot randomized controlled trial evaluated by capsule endoscopy. *Gastrointest Endosc* 2009; 69: 1339-1346 [PMID: 19243767 DOI: 10.1016/j.gie.2008.08.017]
- 32 Higuchi K, Umegaki E, Watanabe T, Yoda Y, Morita E, Murano M, Tokioka S, Arakawa T. Present status and strategy of NSAIDs-induced small bowel injury. *J Gastroenterol* 2009; 44: 879-888 [PMID: 19568687 DOI: 10.1007/s00535-009-0102-2]
- 33 Niwa Y, Nakamura M, Ohmiya N, Maeda O, Ando T, Itoh A, Hirooka Y, Goto H. Efficacy of rebamipide for diclofenac-induced small-intestinal mucosal injuries in healthy subjects: a prospective, randomized, double-blinded, placebo-controlled, cross-over study. *J Gastroenterol* 2008; 43: 270-276 [PMID: 18458842 DOI: 10.1007/s00535-007-2155-4]
- 34 Niwa Y, Nakamura M, Miyahara R, Ohmiya N, Watanabe O, Ando T, Kawashima H, Itoh A, Hirooka Y, Goto H. Geranylgeranylacetone protects against diclofenac-induced gastric and small intestinal mucosal injuries in healthy subjects: a prospective randomized placebo-controlled double-blind cross-over study. *Digestion* 2009; 80: 260-266 [PMID: 19844108 DOI: 10.1159/000236032]
- 35 Iwai T, Ichikawa T, Kida M, Goso Y, Kurihara M, Koizumi W, Ishihara K. Protective effect of geranylgeranylacetone against loxoprofen sodium-induced small intestinal lesions in rats. *Eur J Pharmacol* 2011; 652: 121-125 [PMID: 21130762 DOI: 10.1016/j.ejphar.2010.11.020]
- 36 Dalby AB, Frank DN, St Amand AL, Bendele AM, Pace NR. Culture-independent analysis of indomethacin-induced alterations in the rat gastrointestinal microbiota. *Appl Environ Microbiol* 2006; 72: 6707-6715 [PMID: 17021222 DOI: 10.1128/AEM.00378-06]
- 37 Hagiwara M, Kataoka K, Arimochi H, Kuwahara T, Ohnishi Y. Role of unbalanced growth of gram-negative bacteria in ileal ulcer formation in rats treated with a nonsteroidal anti-inflammatory drug. *J Med Invest* 2004; 51: 43-51 [PMID: 15000255 DOI: 10.2152/jmi.51.43]
- 38 Watanabe T, Higuchi K, Kobata A, Nishio H, Tanigawa T, Shiba M, Tominaga K, Fujiwara Y, Oshitani N, Asahara T, Nomoto K, Takeuchi K, Arakawa T. Non-steroidal anti-inflammatory drug-induced small intestinal damage is Toll-like receptor 4 dependent. *Gut* 2008; 57: 181-187 [PMID: 17639086 DOI: 10.1136/gut.2007.125963]
- 39 Lanas A, Scarpignato C. Microbial flora in NSAID-induced intestinal damage: a role for antibiotics? *Digestion* 2006; 73 Suppl 1: 136-150 [PMID: 16498262 DOI: 10.1159/000089789]
- 40 Davies GR, Wilkie ME, Rampton DS. Effects of metronidazole and misoprostol on indomethacin-induced changes in intestinal permeability. *Dig Dis Sci* 1993; 38: 417-425 [PMID: 8444070]
- 41 Scarpignato C, Dolak W, Lanas A, Matzneller P, Renzulli C, Grimaldi M, Zeitlinger M, Bjarnason I. Rifaximin Reduces the Number and Severity of Intestinal Lesions Associated With Use of Nonsteroidal Anti-Inflammatory Drugs in Humans. *Gastroenterology* 2017; 152: 980-982.e3 [PMID: 28007576 DOI: 10.1053/j.gastro.2016.12.007]
- 42 Watanabe T, Nishio H, Tanigawa T, Yamagami H, Okazaki H, Watanabe K, Tominaga K, Fujiwara Y, Oshitani N, Asahara T, Nomoto K, Higuchi K, Takeuchi K, Arakawa T. Probiotic *Lactobacillus casei* strain Shirota prevents indomethacin-induced small intestinal injury: involvement of lactic acid. *Am J Physiol Gastrointest Liver Physiol* 2009; 297: G506-G513 [PMID: 19589943 DOI: 10.1152/ajpgi.90553.2008]
- 43 Syer SD, McKnight W, Aucouturier A, Martin R, Langella P, Wallace JL. Su1724 Bifidobacteria exert a protective effect against NSAID-induced enteropathy that is dependent on lactate production. *Gastroenterology* 2012; 142: S-489 [DOI: 10.1016/S0016-5085(12)61867-8]
- 44 Montalto M, Gallo A, Curigliano V, D'Onofrio F, Santoro L, Covino M, Dalvai S, Gasbarrini A, Gasbarrini G. Clinical trial: the effects of a probiotic mixture on non-steroidal anti-inflammatory drug enteropathy - a randomized, double-blind, cross-over, placebo-controlled study. *Aliment Pharmacol Ther* 2010; 32: 209-214 [PMID: 20384610 DOI: 10.1111/j.1365-2036.2010.04324.x]
- 45 Endo H, Higurashi T, Hosono K, Sakai E, Sekino Y, Iida H, Sakamoto Y, Koide T, Takahashi H, Yoneda M, Tokoro C, Inamori M, Abe Y, Nakajima A. Efficacy of *Lactobacillus casei* treatment on small bowel injury in chronic low-dose aspirin users: a pilot randomized controlled study. *J Gastroenterol* 2011; 46: 894-905 [PMID: 21556830 DOI: 10.1007/s00535-011-0410-1]
- 46 De Vos P, Mujagic Z, de Haan BJ, Siezen RJ, Bron PA, Meijerink M, Wells JM, Masclee AAM, Boekschoten MV, Faas

- MM, Troost FJ. Lactobacillus plantarum Strains Can Enhance Human Mucosal and Systemic Immunity and Prevent Non-steroidal Anti-inflammatory Drug Induced Reduction in T Regulatory Cells. *Front Immunol* 2017; 8: 1000 [PMID: 28878772 DOI: 10.3389/fimmu.2017.01000]
- 47 Fiorucci S, Antonelli E, Distrutti E, Rizzo G, Mencarelli A, Orlandi S, Zanardo R, Renga B, Di Sante M, Morelli A, Cirino G, Wallace JL. Inhibition of hydrogen sulfide generation contributes to gastric injury caused by anti-inflammatory nonsteroidal drugs. *Gastroenterology* 2005; 129: 1210-1224 [PMID: 16230075 DOI: 10.1053/j.gastro.2005.07.060]
- 48 Wallace JL, Ferraz JG, Muscara MN. Hydrogen sulfide: an endogenous mediator of resolution of inflammation and injury. *Antioxid Redox Signal* 2012; 17: 58-67 [PMID: 22017247 DOI: 10.1089/ars.2011.4351]
- 49 Blackler R, Syer S, Bolla M, Ongini E, Wallace JL. Gastrointestinal-sparing effects of novel NSAIDs in rats with compromised mucosal defence. *PLoS One* 2012; 7: e35196 [PMID: 22496907 DOI: 10.1371/journal.pone.0035196]
- 50 Davies NM, Røseth AG, Appleyard CB, McKnight W, Del Soldato P, Calignano A, Cirino G, Wallace JL. NO-naproxen vs. naproxen: ulcerogenic, analgesic and anti-inflammatory effects. *Aliment Pharmacol Ther* 1997; 11: 69-79 [PMID: 9042976]
- 51 Hawkey CJ, Jones JL, Atherton CT, Skelly MM, Bebb JR, Fagerholm U, Jonzon B, Karlsson P, Bjarnason IT. Gastrointestinal safety of AZD3582, a cyclooxygenase inhibiting nitric oxide donator: proof of concept study in humans. *Gut* 2003; 52: 1537-1542 [PMID: 14570719]
- 52 Blackler RW, Motta JP, Manko A, Workentine M, Bercik P, Surette MG, Wallace JL. Hydrogen sulphide protects against NSAID-enteropathy through modulation of bile and the microbiota. *Br J Pharmacol* 2015; 172: 992-1004 [PMID: 25297699 DOI: 10.1111/bph.12961]
- 53 Ichikawa T, Ota H, Sugiyama A, Maruta F, Ikezawa T, Hotta K, Ishihara K. Effects of a novel histamine H2-receptor antagonist, lafutidine, on the mucus barrier of human gastric mucosa. *J Gastroenterol Hepatol* 2007; 22: 1800-1805 [PMID: 17914953 DOI: 10.1111/j.1440-1746.2006.04721.x]
- 54 Kato M, Kamada G, Yamamoto K, Nishida U, Imai A, Yoshida T, Ono S, Nakagawa M, Nakagawa S, Shimizu Y, Asaka M. Lafutidine prevents low-dose aspirin and loxoprofen induced gastric injury: a randomized, double-blinded, placebo controlled study. *J Gastroenterol Hepatol* 2010; 25: 1631-1635 [PMID: 20880171 DOI: 10.1111/j.1440-1746.2010.06375.x]
- 55 Amagase K, Ochi A, Sugihara T, Kato S, Takeuchi K. Protective effect of lafutidine, a histamine H2 receptor antagonist, against loxoprofen-induced small intestinal lesions in rats. *J Gastroenterol Hepatol* 2010; 25: S111-S118 [PMID: 20586851 DOI: 10.1111/j.1440-1746.2010.06223.x]
- 56 Sano T, Utsumi D, Amagase K, Matsumoto K, Tominaga M, Higuchi K, Takeuchi T, Kato S. Lafutidine, a histamine H2 receptor antagonist with mucosal protective properties, attenuates 5-fluorouracil-induced intestinal mucositis in mice through activation of extrinsic primary afferent neurons. *J Physiol Pharmacol* 2017; 68: 79-90 [PMID: 28456772]
- 57 Kim EH, Lee YC, Chang YW, Park JJ, Chun HJ, Jung HY, Kim HS, Jeong HY, Seol SY, Han SW, Choi MG, Park SH, Lee OJ, Jung JT, Lee DH, Jung HC, Lee ST, Kim JG, Youn SJ, Kim HY, Lee SW. Efficacy of Lafutidine Versus Famotidine in Patients with Reflux Esophagitis: A Multi-Center, Randomized, Double-Blind, Non-inferiority Phase III Trial. *Dig Dis Sci* 2015; 60: 1724-1732 [PMID: 25532503 DOI: 10.1007/s10620-014-3489-4]

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