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Causes and Management of Gastric and Duodenal Ulcer in Adolescents

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Many etiological hypotheses have been suggested to explain the development of peptic ulcers during the last 300 years (including gastric ulcer and duodenal ulcer). In the last two decades, significant progress has been made in understanding the pathophysiology of peptic ulcer disease, particularly with regard to the involvement of Helicobacter pylori and nonsteroidal anti-inflammatory medications (NSAIDs). This study will attempt to review literature on etiology and management of gastric and duodenal ulcers among adolescents.

Keywords: Gastric, ulcer disease; hypotheses; anti-inflammatory.

1. INTRODUCTION

Many individuals have ulceration of the gastric or duodenal mucosa. Both gastric and duodenal ulcers are included in the term peptic ulcer disease (PUC). Reduced efficiency of the stomach mucosal barriers, excessive acid output,

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and infection with Helicobacter pylori bacteria are some of the factors that may lead to ulcer development. PUD is a prevalent condition that affects millions of people each year in the United States. Peptic ulcer illness has a significant financial impact on our health-care system, accounting for about 10% of all medical costs associated with digestive disorders [1]. In the last two decades, significant progress has been made in understanding the pathophysiology of peptic ulcer disease, particularly with regard to the involvement of Helicobacter pylori and nonsteroidal anti-inflammatory medications (NSAIDs). This has resulted in significant modifications in diagnostic and treatment techniques, with the potential to improve clinical outcomes while also lowering health-care expenditures [2].

The geographic distribution of a disease may provide important information about its cause. Similarly, any historical changes in prevalence linked to changes in lifestyle may provide further information. The frequency of ulcers varies throughout the globe, with duodenal ulcers predominating in Western cultures and stomach ulcers being more common in Asia, particularly Japan [3].

A systematic review of the literature regarding the epidemiology of PUD reveals a few key facts. First, it demonstrates that PUD is still a very frequent disorder over the world, with annual incidences ranging from 0.10% to 0.19% for physician-diagnosed PUD and from 0.03% to 0.17% for PUD identified after hospitalisation. Physician-diagnosed PUD had a 1-year frequency of 0.12–1.%, while PUD diagnosed during hospitalizations had a 1-year prevalence of 0.10–0.19% [4]. Their results demonstrate that the prevalence of PUD has reduced in many nations in recent decades, most likely due to a reduction in H. pylori infection, especially in Western populations [4].

However, it is possible that the status in Asian countries is different; a recent study in Korea found that the prevalence of H. pylori infection in people with GU was growing with time, whereas H. Pylori infection in people with DU was declining [5].

The most trustworthy study of physician-diagnosed prevalence came from Sweden, and it used cross-sectional data from the general population to include both symptomatic and asymptomatic PUD [6]. A systematic review reported the total prevalence of PUD was 4.1%, with 19.5% of all PUD cases being asymptomatic [4]. When compared to the lower rates found in other studies of physician-diagnosed PUD in primary care, it appears that a proportion of people with PUD go undetected. Severe consequences, such as gastrointestinal bleeding, may be the initial signs of PUD in people who are asymptomatic. Haemorrhage is linked to a 10% mortality rate and a high rate of recurrence [7].

Over the last few decades, management of H. pylori-associated PUD has vastly improved, culminating in the common use of proton pump inhibitor (PPI)-based triple therapy for H. pylori eradication [8]. However, over this time period, prescriptions for medicines implicated in the aetiology of PUD, such as aspirin and NSAIDs, have also increased, and adherence to gastroprotection for the prevention of NSAID-induced PUD remains far from optimum [9].

2. CAUSES

2.1 Helicobacter Pylori Infection

Helicobacter pylori infection is a prevalent cause of peptic ulcers in adolescents [10]. H. Pylori is linked to both gastric and duodenal ulcer disorders. In the first decade after the discovery of H. pylori, roughly 95 percent of duodenal ulcers and 85%of stomach ulcers were found in the presence of H. pylori infection, according to data from throughout the world [11]. Several cohort studies found that H. pylori-positive participants have a 3 to 10 times higher lifetime risk of ulcer disease than H. pylori-negative individuals, and that 10 to 15% of H. pylori-positive individuals develop ulcer disease throughout long-term follow-up [12]. These findings are based on research conducted in industrialised countries. It's unclear whether H. pylori-positive people in developing nations are at risk for the same diseases. H. pylori eradication regimens concluded the evidence for a causal relationship between H. pylori and ulcer disease by demonstrating that eradication of this bacterium significantly lowered the likelihood of recurrent ulcer illness [13].

A combination of host and bacterial variables promote ulcer formation in the presence of H. pylori. Ulcers are most common where mucosal inflammation is the most severe. This is frequently the gastric transitional zone between corpus and antrum in people with low acid output, which leads to gastric ulcer disease. If

acid output is normal to high, juxta-pyloric and duodenal ulcer disease develops in the distal stomach and proximal duodenum [14].

The rate ratio of antral gastritis for children with H. pylori infection (relative to uninfected individuals) varied from 1.9 to 71.0 in a pooled study of early data (1983-1994), (median, 4.6) [15]. Thus, there was significant evidence for a link between H. pylori infection and antral gastritis and duodenal ulcer in children, but only limited evidence for a link between H. pylori infection and stomach ulcer in adults. Nonetheless, a subsequent retrospective study from Japan (1995-2001) stated that the prevalence of H. pylori was very high in antral (nodular) gastritis and duodenal ulcer (98.5% and 83%, respectively), but it also demonstrated that H. pylori was a definable risk factor for the development of gastric ulcer, despite the fact that infection prevalence did not reach 50%. In the age range of 10-16 years, H. pylori was substantially related to duodenal and stomach ulcers, but not in the age group of 9 years [16].

3. NONSTEROIDAL ANTIINFLAMMA-TORY DRUG-INDUCED GASTRO-DUODENAL INJURY

The two most major independent variables in peptic ulcer disease are nonsteroidal anti-inflammatory drugs (NSAIDs) and H. pylori infection [17]. Their prevalence as a cause of peptic ulcer varies and is linked to the usage of NSAIDs and the prevalence of H. pylori infection in a community [18]. In the senior population, NSAID usage and H. pylori infection are both prevalent.

The use of NSAIDs is becoming a more significant risk factor for PUD. The use of NSAIDs and low-dose aspirin has been linked to an increase in hospitalizations among the elderly owing to peptic ulcer bleeding and perforation. Prescribed NSAIDs account for roughly 25% of all reported adverse medication events in the United States. Every year, around 16500 people with arthritis die as a result of NSAID-related gastrointestinal adverse effects [19]. In developed countries, one fourth of elderly patients use NSAIDs [20,21] (Sayer et al. 2010).

NSAIDs are one of the most frequent causes of medication side effects necessitating hospitalization, particularly among the elderly (Sostres et al. 2009), with significant financial implications [22]. In one Finnish study, 12% of people aged 60 to 74 used prescription NSAIDs on a daily basis, while 9 percent of the same group used both prescribed and over-the-counter (OTC) NSAIDs at the same time [21]. The risk of peptic ulcer bleeding (PUB) among non-aspirin NSAID users is affected by the type of NSAID taken. When compared to ketorolac (Relative Risk (RR) 14.4; 95%CI 5.2-39.9), the risk was found to be lowest when using aceclofenac (2.6; 1.5-4.6), diclofenac (3.1; 2.3-4.2), or ibuprofen (4.1; 3.1-5.3) (Lanas et al. 2006). The use of NSAIDs and acetylsalicylic acid (ASA) together, as well as other bleeding-related medications, increased the risk of PUB (Lanas et al. 2006).

Low-dose ASA alone has been linked to an increased risk of acute upper gastrointestinal bleeding (GIB) [23,24]. When compared to individuals who are H.pylori negative and do not take NSAIDs or low-dose ASA, the risk of PUB in H.pylori positive patients who use NSAIDs is significantly elevated (RR 8.0; 5.0- 13) as well as in patients who just use low-dose ASA (3.5; 2.6-6.1) [25]. Svanes [26], Søreide et al. [27], Chung and Shelat [28] all found that using NSAIDs increases the risk of ulcer perforation. Celecoxib, a selective inhibitor of the cyclo-oxygenase-2 (COX-2) enzyme, was first brought to the market in 1999. The COX-2 selective inhibitors have no effect on the cyclooxygenase-1 (COX-1) enzyme, which is involved in GI mucosal protection and platelet function, but they do prevent inflammation and discomfort caused by prostaglandin production, which is reliant on the COX-2 enzyme. The use of any coxib was not related with PUB (RR 1.5; 95 percent CI 0.9-2.4) in a case-control study conducted in Spain between 2001 and 2004, while the use of rofecoxib marginally raised the risk of PUB (2.1; 1.1-4.0) (Lanas et al. 2006). COX-2 users had a reduced risk of gastroduodenal ulcer complications (RR 0.39; 0.31-0.50) than nonselective NSAID users, according to a Cochrane systematic review of 69 studies [29]. However, growing concerns regarding an elevated risk of cardiovascular adverse effects among COX-2 selective NSAID users [30] led to the recall of rofecoxib in 2004 and valdecoxib the following year. In a more recent study, there was no difference in the risk of cardiovascular events between COX-2 users and conventional NSAID users, except in individuals who used naproxen, for whom there was no increased risk of cardiovascular events [31]. Patients who were hospitalized for PUB and needed both ASA and NSAID treatment for comorbidities were randomly assigned to continued medication of

celecoxib + esomeprazol or naproxen + esomeprazol in a recent Hong Kong research to compare the incidence of rebleeding [32]. With no difference in cardiovascular events, naproxen users had a substantially greater cumulative incidence of rebleeding.

4. OTHER DRUGS

In a Danish population-based case-control research, the use of selective serotonin reuptake inhibitors (SSRIs) was linked to a slightly higher incidence of PUB (or hemorrhagic gastritis). The precise mechanism by which an SSRI affects the risk of bleeding is unclear, although its capacity to suppress platelet aggregation and increase stomach acid production are two possibilities [33].

Calcium channel blockers (RR 1.6; 95%CI 1.5-1.6), nitrates (2.6; 2.4-2.7) and aldosterone antagonists (3.3; 3.1-3.5) were shown to enhance the incidence of acute upper GIB in a large international study [34].

5. OTHER RISK FACTORS

PUD and associated consequences are more common as people become older [26]. A prior history of PUD is a strong predictor of recurrence [25]. In Spain, female gender was associated with a lower incidence of PUB (Lanas et al. 2006), whereas in Korea, male gender was associated with a higher risk of PUB [35]. PUD is made more likely by smoking (Aro et al. 2006, Lanas et al. 2006) [25]. In Finland, smoking was a dose-dependent risk factor for PUB, while alcohol use was not [36]. In Asia, findings contradicting those of the Finnish research have been published, with alcohol consumption linked to PUB but no link identified between smoking and PUB [35,37]. It has also been shown that smoking is a risk factor for ulcer perforation [26]. In a Swedish population-based research, obesity was linked to an increased incidence of simple stomach ulcer (Aro et al. 2006). Psychological stress and abrupt changes in living circumstances, such as witnessing a life-threatening earthquake or being housed in a refugee shelter, have been linked to the development of PUD in recent research [38, 39, 40]. Until recently, the use of gastroprotective agents, such as PPIs, as stress ulcer prophylaxis in all critically ill patients in intensive care units was standard practice, despite concerns about its necessity for all patients and potential side effects (nosocomial pneumonia, Clostridium difficile infection, or cardiovascular events) [41].

6. MANAGEMENT OF GASTRIC AND DUODENAL ULCERS

Patients with acute peptic ulcer bleeding or perforation should be evaluated as soon as possible and resuscitated before receiving final treatment. A rigorous strategy for blood transfusions is recommended by international standards, with a hemoglobin goal level of 70 g/l [42]. When all the patients hospitalized with severe acute upper GIB in Spain were analyzed, there was a tendency toward improved survival among PUB patients with restricted strategies, but it was not statistically significant [43].

A difficult clinical issue is coagulopathy and acute bleeding. The precise goal level for the International Normalized Ratio (INR) of coagulation has not been established, and it should be determined based on the particular patient's cause for anticoagulation or the presence of disease-causing coagulopathy [44]. It is strongly advised that risk stratification scores be used [42]. When predicting rebleeding or death in PUB patients, the pre- and post-endoscopic Rockall scores, the Glasgow Blatcford score, or a newer AIMS65 score are useful for separating patients into low- and high-risk groups [45,46].

In the treatment of PUD patients, gastroprotective agents (GPAs) and endoscopic therapies are critical, while surgery is required in instances of refractory bleeding or perforation. Interventional radiology is increasingly being used in PUB, particularly in patients who are too frail to undergo surgery.

7. GASTROPROTECTIVE AGENTS (GPAs)

The use of GPAs, particularly proton pump inhibitors (PPIs), has risen in recent decades [47,48]. The PPIs are used to maintain a neutral stomach pH, which is favouring clot formation. GPAs such as H2-receptor antagonists, antacids, misoprostol, sucralfate, and alginic acids are currently used in small amounts compared to PPIs [49]. PPI usage is linked to a lower risk of bleeding as a complication of PUD [RR 0.3; 95%CI 0.3-0.4 (Lanas et al. 2006), RR 0.4; 0.3-0.6 [25]]. The use of a PPI in conjunction with an ASA or an NSAID decreased the risk of bleeding (Lanas et al. 2007). However, in a multinational

European trial [34], monotherapy use of GPA was linked with a modestly higher risk of acute upper. The use of GPA is ineffective for preventing bleeding in individuals who have a number of recognized risk factors. Patients with high-risk stigmata of ulcer bleeding should get continuous intravenous PPI therapy for the next 72 hours after the index endoscopy, according to worldwide recommendations [42,50].

8. TREATMENT OF H. pylori

To eliminate H. pylori infection, a one-week combination treatment of two antimicrobials (amoxicillin, clarithromycin, tetracycline, or metronidazole) plus a PPI is generally suggested [51]. At least 80% of patients should respond to the first-line eradication treatment [52]. In vitro metronidazole resistance, on the other hand, does not necessarily imply therapeutic failure. Because of the rising frequency of antibiotic resistance throughout the globe, a prolonged 10-day or two-week treatment is now advised [53,52]. Susceptibility testing may be useful in the treatment of H.pylori infection when first-line eradication medication has failed.

9. ENDOSCOPIC INTERVENTION

For ulcers with active bleeding, a non-bleeding visible artery, or an adhering clot (Forrest Ia-IIb), endoscopic treatment is indicated to reduce the risk of recurrent bleeding. Some studies recommend removing an adherent clot (IIb) in the search for an artery, and endoscopic treatment should only be used if one is found [44]. Endoscopic treatment is not required in patients with haematin on the ulcer base (IIc) or a clean base ulcer (III). Dual treatment with epinephrine injection is suggested by worldwide recommendations to reduce the risk of rebleeding, surgery, and death [42,50]. Injection, heat, and mechanical techniques of endoscopic therapy have historically been used. Endoscopic topical hemostatic powders have recently been available on the market [54]. However, several national audits have shown that the percentage of patients getting dual treatment for significant stigmata of hemorrhages is as low as 34% in Canada, 35% in Italy, and 38% in the United Kingdom [55], (Barkun et al. 2004).

10. SURGICAL TREATMENT

Because of effective conservative therapies, the necessity for elective surgery has reduced significantly [56]. However, perforated ulcers and refractory rebleedings still need emergency surgery. As observed in Western nations, the necessity for emergency surgery due to PUB in Sweden dropped substantially between 1987 and 2004, while the use of endoscopic therapies rose [57,44]. Only 1.3% of PUB patients required surgery, according to a new research from the Netherlands [58]. In acute PPU patients, the superiority of open versus laparoscopic surgery is debatable. There was no statistically significant difference in complications or death between the open and laparoscopic techniques in a Cochrane systematic review of three randomised clinical trials on PPU patients with repair using an omentum patch or fibrin sealant [59].

11. TAE

TAE is an option for individuals with severe and recurring bleeding who do not respond to endoscopic treatment. There are no prospective randomized controlled trials comparing surgery with TAE. When compared to surgery, TAE is linked with greater rebleeding rates with no significant difference in mortality, although patients admitted to TAE were considerably older and may not have been surgical candidates owing to comorbidities [60]. Patients underwent TAE had fewer postoperative complications, but no difference in rebleeding rate or mortality [61], while TAE use among endoscopy-refractory PUB patients in Denmark was linked to a lower 30-day mortality rate than surgical haemostasis [61,62].

12. CONCLUSION

Persistent H. pylori infection, prolonged use of NSAIDs, severe comorbidities that impede ulcer healing, or other diseases such as gastrinoma or stomach cancer are also frequent causes. Patients may be candidates for surgical therapy if the ulcer persists after addressing the aforementioned risk factors. Vagotomy or partial gastrectomy are two surgical alternatives.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. WHO disease and injury country estimates". World Health Organization; 2009. Retrieved Jun. 11, 2021.
2. Feinstein LB, Holman RC, Christensen KLY, Steiner CA, Swerdlow DL. Trends in hospitalizations for peptic ulcer disease, United States, 1998–2005. Emerging Infectious Diseases. 2010;16(9):1410.
3. Graham DY. History of Helicobacter pylori, duodenal ulcer, gastric ulcer and gastric cancer. World J Gastroenterol. 2014;20(18):5191-204.
4. Sung JJ, Kuipers EJ, El-Serag HB. Systematic review: The global incidence and prevalence of peptic ulcer disease. Alimentary Pharmacology and Therapeutics. 2009;29(9):938-46.
5. Testerman TL, Morris J. Beyond the stomach: An updated view of Helicobacter pylori pathogenesis, diagnosis, and treatment. World J Gastroenterol. 2014;20(36):12781-12808. DOI:10.3748/wjg.v20.i36.12781.
6. Huang SC, Sheu BS, Lee SC, Yang HB, Yang YJ. Etiology and treatment of childhood peptic ulcer disease in Taiwan: A single center 9-year experience. J Formos Med Assoc. 2010;109(1):75-81.
7. Narayanan M, Reddy KM, Marsicano E. Peptic ulcer disease and Helicobacter pylori infection. Mo Med. 2018;115(3):219-224.
8. Pourfarzi F, Zahirian Moghadam T, Zandian H, Malekzadeh R, Yazdanbod A. Cost-effectiveness analysis of two routine therapeutic methods for Helicobacter pylori eradication: A Persian cohort-based study. Gastroenterol Hepatol Bed Bench. 2021;14(3):250-259.
9. Abraham NS, El–Serag HB, Johnson ML, Hartman C, Richardson P, Ray WA, Smalley W. National adherence to evidence-based guidelines for the prescription of nonsteroidal anti-inflammatory drugs. Gastroenterology. 2005;129(4):1171-8.
10. Albaqawi ASB, El-Fetoh NMA, Alanazi RFA, Alanazi NSF, Alrayya SE, Alanazi ANM, Alenezi SZT, Alanazi RAA, Alshalan AM, Alenezi OT, Ali WMB. Profile of peptic ulcer disease and its risk factors in Arar, Northern Saudi Arabia. Electron Physician. 2017;9(11):5740-5745.
11. Kavitt R, Lipowska A, Anyane-Yeboa A, et al. Diagnosis and treatment of peptic ulcer disease. Am J Med. 2019;132(4):447–456.
12. Schöttker B, Adamu MA, Weck MN, Brenner H. Helicobacter pylori infection is strongly associated with gastric and duodenal ulcers in a large prospective study. Clin Gastroenterol Hepatol. 2012;10(5):487-93.
13. He C, Chen M, Liu J, Yuan Y. Host genetic factors respond to pathogenic step-specific virulence factors of Helicobacter pylori in gastric carcinogenesis. Mutat Res Rev Mutat Res. 2014;759:14-26.
14. Van Zanten SJ, Dixon MF, Lee A. The gastric transitional zones: neglected links between gastroduodenal pathology and helicobacter ecology. Gastroenterology. 1999;116(5):1217-29.
15. Macarthur C, Saunders N, Feldman W. Helicobacter pylori, gastroduodenal disease, and recurrent abdominal pain in children. Jama. 1995;273(9):729-34.
16. Kato S, Nishino Y, Ozawa K, Konno M, Maisawa SI, Toyoda S, Tajiri H, Ida S, Fujisawa T, Iinuma K. The prevalence of Helicobacter pylori in Japanese children with gastritis or peptic ulcer disease. Journal of Gastroenterology. 2004;39(8):734-8.
17. Higham J, Kang JY, Majeed A. Recent trends in admissions and mortality due to peptic ulcer in England: Increasing frequency of haemorrhage among older subjects. Gut. 2002;50(4):460-4.
18. Weil J, Colin-Jones D, Langman M, Lawson D, Logan R, Murphy M, Rawlins M, Vessey M, Wainwright P. Prophylactic aspirin and risk of peptic ulcer bleeding. Bmj. 1995;310(6983):827-30.
19. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, Day R, Ferraz MB, Hawkey CJ, Hochberg MC, Kvien TK. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. New England Journal of Medicine. 2000;343(21):1520-8.
20. Barat I, Andreasen F, Damsgaard EMS. The consumption of drugs by 75 year old individuals living in their own homes. Eur J Clin Pharmacol. 2000;56:501-509.
21. Turunen JHO, Mäntyselkä PT, Kumpusalo EA, Ahonen RS. Frequent analgesic use at population level: Prevalence and patterns of use. Pain. 2005;115:374-81.

22. Laine L. Gastrointestinal effects of NSAIDs and coxibs. J Pain Symptom Manage. 2003;25:32-40.
23. Hallas J, Dall M, Andries A, Andersen BS, Aalykke C, Hansen J, Andersen M, Lassen AT. Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: Population based control-case study. BMJ. 2006;333:726-730.
24. García Rodrígues LA, Lin KJ, Hernández-Díaz S, Johansson S. Risk of upper gastrointestinal bleeding with low-dose acetylsalicylic acid alone and in combination with chlopidogrel and other medications. Cirucaltion. 2011;123:1108-1115.
25. Sostres C, Carrera-Lasfuentes P, Benito R, Roncales P, Arruebo M, Arroyo MT, Bujanda L, García-Rodríguez LA, Lanas A. Peptic ulcer bleeding risk. The role of Helicobacter pylori infection in NSAID/low-dose aspirin users. Am J Gastroenterol. 2015;110:684-689.
26. Svanes. Trends in perforated peptic ulcer: Incidence, etiology, treatment, and prognosis. World J Surgery. 2000;24:277-283.
27. Søreide K, Thorsen K, Søreide JA. Strategies to improve the outcome of emergency surgery for perforated peptic ulcer. Br J Surg. 2014;101:51-64.
28. Chung KT, Shelat VG. Perforated peptic ulcer – An update. World J Gastrointest Surg. 2017;9(1):1-12.
29. Rostom A, Muir K, Dubé C, Jolicoeur E, Boucher M, Joyce J, Tugwell P, Wells GW. Gastrointestinal safety of cyclooxygenase-2 inhibitors: A cochrane systematic review. Clin Gastroenterol Hepatol. 2007;5:818-828.
30. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA. 2001;286:954-959.
31. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. BMJ. 2006;332:1302-1308.
32. Chan FKL, Ching JYL, Tse YK, Lam K, Wong GLH, Ng SC, Lee V, Au KWL, Cheong PK, Suen BY, Chan H, Kee KM, Lo A, Wong VWS, Wu JCY, Kyaw MH. Gastrointestinal safety of celecoxib versus naproxen in patients with cardiothrombotic disease and arthritis after upper gastrointestinal bleeding (CONCERN): An industry-independent, double-blind, double-dummy, randomised trial. Lancet. 2017;389:2375-2382.
33. Jiang HY, Chen HZ, Hu XJ, Yu ZH, Yang W, Deng M, Zhang YH, Ruan B. Use of selective serotonine reuptake inhibitors and risk of upper gastrointestinal bleeding: A systemic review and meta-analysis. Clin Gastroenterol Hepatol. 2015;13:42-50.
34. Masclee GMC, Valkhoff VE, Coloma PM, de Ridder M, Romio S, Schuemie MJ, Herings R, Gini R, Mazzaglia G, Picelli G, Scotti L, Pedersen L, Kuipers EJ, van der Lei J, Sturkenboom MCJM. Risk of upper gastrointestinal bleeding from different drug combinations. Gastroenterol. 2014;147:784-792.
35. Kang JM, Kim N, Lee BH, Park HK, Jo HJ, Shin CM, Lee SH, Park YS, Hwang JH, Kim JW, Jeong S-H, Lee DH, Jung HC, Song IS. Risk factors for peptic ulcer bleeding in terms of Helicobacter pylori, NSAIDs, and antiplatelet agenst. Scand J Gastroenterol. 2011;46:1295-1301.
36. Udd M, Miettinen P, Palmu A, Heikkinen M, Janatuinen E, Pasanen P, Tarvainen R, Mustonen H, Julkunen R. Analysis of the risk factors and their combinations in acute gastroduodenal ulcer bleeding: A case-control study. Scand J Gastroenterol. 2007;42:1395-1403.
37. Nagata N, Niikura R, Sekine K, Sakurai T, Shimbo T, Kishida Y, Tanaka S, Aoki T, Okubo H, Watanabe K, Yokoi C, Akiyama J, Yanase M, Mizokami M, Uemura N. Risk of peptic ulcer bleeding associated with Helicobacter pylori infection, nonsteroidal anti-inflammatory drugs, low-dose aspirin, and antihypertensive drugs: A case-control study. J Gastroenterol Hepatol. 2015;30:292-298.
38. Malfertheiner P, Chan FKL, McColl KEL. Peptic ulcer disease. Lancet. 2009;374:1449-1461.
39. Yamanaka K, Miyatani H, Yoshida Y, Asabe S, Yoshida T, Nakano M, Obara S, Endo H. Hemorrhagic gastric and duodenal ulcers after the Great East Japan earthquake disaster. World J Gastroenterol. 2013;19:7426-7432.
40. Levenstein S, Rosenstock S, Jacobsen RK, Jorgensen T. Psychological stress increases risk for peptic ulcer, regardless

of Helicobacter pylori infection or use of nonsteroidal anti-inflammatory drugs. Clin Gastroenterol Hepatol. 2015;13:498-506.

41. Marker S, Krag M, Møller MH. What´s new with stress ulcer prophylaxis in the ICU? Intensive Care Med. 2017;43:1132-1134.
42. Barkun AN, Bardou M, Kuipers EJ, Sung J, Hunt RH, Martel M, Sinclair P. For the international consensus upper gastrointestinal bleeding conference group. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. Ann Intern Med. 2010;152:101-113.
43. Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, Graupera I, Poca M, Alvarez-Urturi C, Gordillo J, Guarner-Argante C, Santaló M, Muñiz E, Guarner C. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013;368:11-21.
44. Lau JYW, Barkun A, Fan D-M, Kuipers EJ, Yang Y-S, Chan FKL. Challenges in the management of acute peptic ulcer bleeding. Lancet. 2013;381:2033-2043.
45. Rockall TA, Logan RFA, Devlin HB, Northfielg. Risk assessment after acute upper gastrointestinal hemorrhage. Gut. 1996;38:316-321.
46. Saltzman JR, Tabak YP, Hyett BH, Sun X, Travis AC, Johannes RS. A simple risk score accurately predicts in-hospital mortality, length of stay, and cost in acute upper GI bleeding. Gastrointest Endosc. 2011;74(6):1215-1224.
47. Pérez-Aisa MA, del Pino D, Siles M, Lanas A. Clinical trens in ulcer diagnosis in a population with high prevalence of Helicobacter pylori infection. Aliment Pharmacol Ther. 2005;21:65-72.
48. Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in prescription drug use among adults in the United States from 1999-2012. JAMA. 2015;314:1818-1831.
49. Finnish Medicines Agency Fimea and Social Insurance Institution.Finnish statistics on medicines 2015; 2016.
Available:http://www.kela.fi/tilastojulkaisut_suomenlaaketilasto.
50. Gralnek IM, Dumonceau JM, Kuipers JE, Lanas A, Sanders DS, Kurien M, Rotandano G, Hucl T, Dinis-Ribeiro M, Marmo R, Racz I, Arezzo A, Hoffmann RT, Lesur G, de Franchis R, Aabakken L, Veitch A, Radaelli F, Salgueiro P, Cardoso R, Maia L, Zullo A, Cipoletta L, Hassan C. Diagnosis and management of acute nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy. 2015;47:1-46.
51. Working group appointed by the finnish medical society duodecim and the finnish society of gastroenterology (Höckerstedt K, Ashorn M, Heikkinen M, Karvonen AL, Koskenpato J, Laukkala T, Niemelä S, Rasmussen M, Scheinin T, Sipilä R, Voutilainen M); 2013.
Available:www.kaypahoito.fi.
52. Malfertheiner P, Megraud F, O´Morain C, Gispert JP, Kuipers EJ, Axon ATR, Bazzoli F, Gasbarrini A, Atherton J, Graham DY, Hunt R, Moayyedi P, Rokkas T, Rugge M, Selgrad M, Suerbaum S, Sugano K, El-Omar EM. On behalf of the European Helicobacter and Microbiota study group and consensus panel. Management of Helicobacter pylori infection – the Maastricht V/Florence consensus report. Gut. 2017;66:6-30.
53. Lanas A, Chan FKL. Peptic ulcer disease. Lancet. 2017;390:613-624.
54. Lu Y, Chen YI, Barkun A. Endoscopic management of acute peptic ulcer bleeding. Gastroenterol Clin N Am. 2014;43:677-705.
55. Hearnshaw SA, Logan RF, Lowe D, Travis SPL, Murphy MF, Palmer KR. Use of endoscopy for management of acute upper gastrointestinal bleeding in the UK: Results of a nationwide audit. Gut. 2010;59:1022-1029.
56. Paimela H, Paimela L, Myllykangas-Luosujärvi R, Kivilaakso E. Current features of peptic ulcer disease in Finland: Incidence of surgery, hospital admissions and mortality for the disease during the past twenty-five years. Scand J Gastroenterol. 2002;37:399-403.
57. Sadic J, Borgström A, Manjer J, Toth E, Lindell G. Bleeding peptic ulcer – time trends in incidence, treatment and mortality in Sweden. Aliment Pharmacol Ther. 2009;30:392-398.
58. De Groot NL, van Oijen MGH, Kessels K, Hemmink M, Weusten BLAM, Timmer R, Hazen WL, van Lelyveld N, Vermeijden RR, Curvers WL, Baak BC, Verburg R, Bosman JH, de Wijkerslooth LRH, de Rooij J, Venneman NG, Pennigs M, van Hee K, Scheffer BCH, van Eijk RL, Meiland R, Siersema PD, Bredenoord AJ.

Reassessment of the predictive value of the Forrest classification for peptic ulcer rebleeding and mortality: Can classification be simplified? Endosc. 2014;46:46-52.
59. Sanabria A, Villegas MI, Morale Uribe CH. Laparoscopic repair for perforated peptic ulcer disease. Cochrane Database of Systematic Reviews. 2013;2. Art.No.:CD004778.
60. Beggs AD, Dilworth MP, Powell SL, Atherton H, Griffiths EA. A systematic review of transarterial embolisation versus emergency surgery in treatment of major nonvariceal upper gastrointestinal bleeding. Clin Exp Gastroenterol. 2014;7:94-104.
61. Nykänen T, Peltola E, Kylänpää L, Marianne U. Bleeding gastric and duodenal ulcers: Case-control study comparing angioembolization and surgery. Scand J Gastroenterol. 2017;52:523-530.
62. Sayer GP, Britt H, Horn F, Bhasale A, McGeechan K, Charles J, Miller GC, Hull B, Scahill S. Measures of health and health care delivery in general practice in Australia. Australian Institute of Health and Welfare; 2000.
Available:www.aihw.gov.au.

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