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Case Report

EPIGASTRIC PAIN

Juniarto Mende[1]*, Cindy Elvionita[2], Rachmi Nurkhalika[3], Miranda Taborat[1], Mariyo Jane Sanggel[1], Ezra Pasaribu[1]

[1]*Program Studi Farmasi, Sekolah Tinggi Ilmu Kesehatan Papua*
[2]*Program Studi Farmasi Klinik, Fakultas Ilmu Kesehatan, Universitas Baiturrahmah*
[3]*Program Studi Farmasi, Fakultas Ilmu Kesehatan, Universitas Malahayati*

Email Corresponding:
juniarto.mende97@gmail.com

Page : 79-88

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ABSTRAK

Pasien laki-laki (76 tahun) datang dengan keluhan nyeri uluh hati dari tadi malam, skala nyeri 7 sampai dengan 8 (sangat mengganggu). Pemeriksaan tanda-tanda vital didapatkan peningkatan tekanan darah dan kondisi pasien masih mengalami nyeri perut dan atau uluh hati yang. Awal masuk didiagnosis adalah *epigastristis pain*. Pemeriksaan gastrocopy didapatkan multipel nodul di perbatasan corpus dan fundus, antral gastritis erosif dan hipotoni pylori. Pada pemeriksaan patologi anatomi didapatkan hasil mukosa Gaster: Radang kronis granulatif, proliferatif degeneratif. Pemeriksaan penunjang terdapat penurunan kadar hemoglobin, hematokrit, dan natrium. Diagnosisi utama adalah anthral gastritis erosiva. Diagnosia sekunder adalah hipotoni pylori, hipertensi, hipertiroid dan hiponatremia. Terapi yang diberikan cliad (clidium/chlordiazepoxide) 1 tab/8 jam, infus NaCl 3% 100 mL/24 jam, alprazolam 1 tab/24 jam, injeksi pantoprazole 1 amp/24 jam, rebamipide 1 tab/8 jam, amlodipin 1 tab/24 jam, thyrozol ½ tab/24 jam, amitriptilline 1 tab/12 dan lioresal 10 mg/12 jam. Edukasi yang diberikan seperti menghindari dan mengubah pola makan atau minum seperti makanan pedas, dan minuman kopi. Makan lebih sedikit, lebih sering daripada 2 atau 3 kali makan besar. Farmasis berperan penting dalam memonitoring skala nyeri nyeri uluh hati dan kadar natrium

ABSTRACT

A male patient (76 years) complained of heartburn since last night, pain scale of 7 to 8 (very disturbing). Examination of vital signs found increased blood pressure, and the patient's condition was still experiencing abdominal pain and or heart ulcers. The early admission diagnosis was epigastric pain. Gastroscopy examination revealed multiple nodules on the border of the corpus and fundus, antral erosive gastritis and hypotonia pylori. On anatomic pathological study, gastric mucosa results were obtained: Granulative chronic inflammation, degenerative proliferative. Investigations showed a decrease in hemoglobin, hematocrit, and sodium levels. The main diagnosis is anthral erosive gastritis. Secondary diagnoses are hypotonia pylori, hypertension, hyperthyroidism and hyponatremia. Therapy given cliad (clidium/chlordiazepoxide) 1 tab/8 hours, infusion of 3% NaCl 100 mL/24 hours, alprazolam one tab/24 hours, injection of pantoprazole 1 amp/24 hours, rebamipide one tab/8 hours, amlodipine one tab /24 hours, thyrozol ½ tab/24 hours, amitryptiline one tab/12 and lioresal 10 mg/12 hours. Education is provided, such as avoiding and changing eating or drinking patterns like spicy foods and coffee drinks. Eat smaller meals more often than 2 or 3 large meals. Pharmacists play an important role in monitoring heartburn pain scales and sodium levels.

INTRODUCTION

Globally, around 10-20% suffer from chronic functional disorders in the upper gastrointestinal tract [1]. Dyspepsia and symptoms related to stomach ulcers occur between 15% to 40% of the population [2].

Nearly 80% of dyspepsia patients who go to the hospital are dyspepsia functional [3].

Study in Brazil, as many as 548 people had a prevalence of functional dyspepsia of 10.6% consisting of 8.2% postprandial discomfort syndrome and 2.4% epigastric pain [2]. A nationwide multicenter prospective study in Korea found 10.3% experienced functional dyspepsia and composed of 4.8% of the subtypes of postprandial distress syndrome alone, 3.0% of epigastric pain syndrome alone, and 2.5% of postprandial distress syndrome epigastric pain syndrome overlap [4].

Functional dyspepsia is a complex disorder with symptoms such as postprandial fullness, early satiety, burning or pain in the epigastrium, discomfort in the upper abdomen, nausea, vomiting and bloating [5,6]. Other factors related to the onset of symptoms are delayed gastric emptying, impaired accommodation of the proximal stomach, abnormal gastric acid secretion, visceral hypersensitivity and psychological factors [6].

This should identify potential causes of symptoms such as gastroesophageal reflux disease (GERD), peptic ulcer disease and drug side effects [7]. Because these disorders are not fatal but can reduce the quality of life and become a social burden on society[8]. In addition, patients' dyspepsia incurs high direct and indirect costs and work productivity is disrupted by dyspeptic symptoms[9]. The purpose of this case report is to research; the authors describe an issue related to epigastric pain and its management according to the existing literature.

MATERIALS AND METHODS

The reported case is a case of Epigastric Pain written through a case report. This case report writing is done descriptively by examining a problem through a case that consists of one unit. Cases were taken through medical records by monitoring the progress of the patient's condition from the start until the patient improved and was allowed to go home. The case studies studied were only in the form of therapy that the patient received, was appropriate or not. The case studies were only in the form of a single entity but were analyzed in depth for both clinical outcomes and did not cause unwanted side effects.

RESULTS

On examination, the patient's vital signs, namely breathing, pulse and temperature, were within the normal range. Blood pressure results fluctuate within the normal range. The patient's condition, such as abdominal pain or heartburn, goes up and down with a pain scale ranging from two to seven. On routine blood investigations, a decrease in hemoglobin was found to be 11.8 g/dL (normal 13.2-17.3 g/dL), hematocrit 34% (normal 40-54%), sodium 123.1 mmol/L and 130.8 mmol/L (normal 136-146 mmol/L).

Based on the gastroscopy examination performed by the patient, the esophageal mucosa was normal, with multiple nodules on the border of the fundus and corpus. There is erosion in the antrum, pylori gaping, and bile reflux +. The bulb and descending duodenum are normal. It can be concluded that regarding the gastroscopy examination, there are multiple nodules on the border of the corpus and fundus, antral erosive gastritis and hypotonia pylori. The results of a gastroscopy examination can be seen in Figure 1.

Anatomical, pathological examination obtained results macroscopically obtained material without description: two small pieces of tissue stuck to paper with a diameter of 0.3 cm, all white printing. Sub epithelium, hyperplastic glands, dilated lumen, glandular epithelial cells mostly degenerate; fibrotic stroma, some vascular vasodilatative bleeding, with a small lymphocyte precipitate. There were no typical and malignant signs. It can be concluded that gastric mucosa: chronic

granulative inflammation, degenerative proliferative.

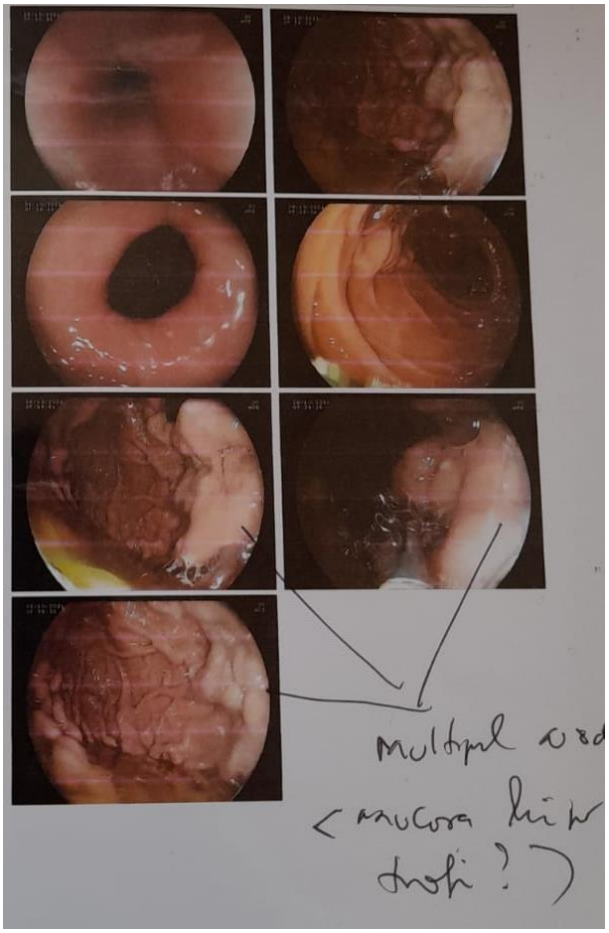

Figure 1. Gastrocopy Examination Result

DISCUSSION

A 76-year-old man came to Bethesda Hospital Yogyakarta with complaints of heartburn last night, a pain scale of 7-8 (very disturbing). Past medical history is an ulcer. The history of drug administration was amlodipine 5 mg/day. The patient has no drug allergies. The patient was diagnosed early with epigastritis pain, and the main diagnosis was erosive antral gastritis. Secondary or comorbid diagnoses are hypotonia pylori, hypertension, hyperthyroidism and hyponatremia. The therapy the patient received was cliad (clidium/chlordiazepoxide) 1 tab/8 hours, an infusion of 3% NaCl 100 mL/24 hours for 7 days; alprazolam 1 tab/24 hours, pantoprazole injection 1 amp/24 hours, rebamipide 1 tab/8 hours and thyrozol ½ tab/24 hours for 6 days; amitriptilline 1 tab/12 for 5 days; lioresal 10 mg/12 hours for 2 days.

Gastritis is characterized by epigastric pain like burning or gnawing [10]. The leading causes of dyspepsia include GORD (gastroesophageal reflux disease), chronic peptic ulcer disease, gastric cancer and other malignancies, gallstones, medications, and functional dyspepsia. Risk factors for patients with dyspepsia are previous history of peptic ulcer disease, age > 60 years, high doses or long-term use of NSAIDs, peptic ulcer disease infected with Helicobacter pylori, chronic alcohol use, smoking habits, stress and depression [11]. The optimal management strategy is to provide empiric therapy for 1-4 weeks. Drugs that can be used are antacids, gastric acid antisecretory agents such as PPIs or H2 receptor antagonists (H_2RA), prokinetics and cytoprotection (such as rebamipide) [12]. Patients with epigastric pain syndrome (EPS) subtype can be treated with proton pump inhibitors (PPIs). In contrast, patients with postprandial distress syndrome (PDS) can be treated with prokinetics, and patients with EPS and PDS can be given PPIs and prokinetics [13].

The patient received the drug pantoprazole injection 1 amp/24 hours for six days. A double-blinded study showed that intravenous pantoprazole helped and stopped dyspeptic symptoms in 30 to 60 minutes in the emergency department [14]. The use of the proton pump inhibitor (PPI) group is viewed from its effectiveness, namely the recovery of vomiting, nausea and freedom from abdominal pain [15]. Research by Khatir et al. [16] states that a comparison of the two groups of pantoprazole and ranitidine intravenously after treatment showed that there was a significant difference in the severity of pain between the two treatment groups ($p < 0.001$). Pantoprazole effectively improves initial epigastric pain [16]. Reports from Wang et al. [17] involving 3725

patients stated that PPIs were more effective than placebo for reducing symptoms in patients with functional dyspepsia (RR = 10.3; 95% Cl, 2,7-17,3). PPIs are effective against epigastric pain syndrome (EPS) and evaluate symptom reduction in patients with functional dyspepsia [18]. The results of 25 RCTs (randomized controlled trials) found that low-dose PPIs have the same efficacy as standard PPI doses. Therefore PPI is more effective than placebo in relieving dyspeptic symptoms in functional dyspepsia patients (RR 0.82; 95% Cl 0.82-0.94) [19]. Report from Suyata et al., [20] Omeprazole is more effective than rebamipide in improving NSAID-induced gastropathy and as safe as rebamipide in treating NSAID-induced gastropathy.

Administration of rebamipide one tab/8 hours for six days. Rebamipide is a 2(1H)-quinolinone amino acid derivative and has been used for mucosal protection, healing of gastroduodenal ulcers, and treatment of gastritis [21]. The mechanism of rebamipide is to treat gastritis (irritation, inflammation, or erosion of the stomach lining) and stomach ulcers. Mucosal protective agent increases gastric blood flow, promotes prostaglandin biosynthesis, and reduces free radicals [22]. Rebamipide showed improved clinical symptoms (distension, upper stomach acid reflux, belching, loss of appetite [23]. Another report showed that a combination of a proton pump inhibitor (PPI) plus rebamipide was more effective than the PPI group in treating ulcers larger than 20 nm for 28 days [24]. The study involved 1227 patients consisting of 631 patients who were given rebamipide and 596 patients who were not given rebamipide. Adding rebamipide to the eradication regimen significantly increased the effectiveness of treatment ($p < 0.001$) [25].

The study by Takayama et al. [26] stated that rebamipide treatment was more cost-effective and prevented granulation lesions after ulcer healing. Rebamipide or PPI treatment has a similar ulcer healing rate in ESD (endoscopic submucosal dissection) patients [26]. Triple blind randomized study at RSUP Dr. Mohammad Hoesin Palembang found that rebamipide was as effective as omeprazole in improving symptoms [20]. Research by El-Zahaby et al., [27] showed that rebamipide had a better protective effect than pantoprazole in preventing injury to the gastric mucosa induced by Dexamethasone in rats.

Administration of cliad (clidium/chlordiazepoxide) 1 tab/8 hours for 7 days. Cliad contains the drug clidium/chlordiazepoxide and is an adjunct therapy for proton pump inhibitors (PPI) for patients with refractory dyspepsia. Another report showed that the aluminum/chlordiazepoxide group improved overall quality of life compared to the placebo group. This combination can be used as an additional therapy in patients with functional dyspepsia without any major side effects [28].

Amitriptyline 1 tab/12 hours for 5 days. A study by Liu *et al*., showed that after 4 weeks of treatment, the amitriptyline group experienced a significant decrease in the Nepean Dyspepsia Index (NDI) score and the severity and disorder of the epigastric pain syndrome compared to the pantoprazole group ($p < 0.05$) [29]. Another report stated that amitriptyline slowed oral transit time (OCTT) ($p < 0.05$) but did not affect gastric emptying and did not affect the proximal stomach. Administration of amitriptyline at low doses effectively improves dyspeptic symptoms and sleep time in epigastric pain syndrome (EPS) patients, although it does not reduce psychological distress [29,30].

The patient received Lioresal (baclofen) 10 mg/12 hours for 2 days. According to Liu *et al*., baclofen effectively reduces the pain response in an experimental model of functional dyspepsia through a GABA receptor agonist mechanism[31]. The patient received alprazolam 1 tablet/24 hours.

The results of the information obtained from the patient's family said that the patient had difficulty sleeping. A cross-sectional study at Hasanuddin University Hospital found that using alprazolam improved sleep quality, both short and long-term use[32].

Based on information from the patient's child, the patient likes to eat spicy and sour food. The education is to avoid and change eating or drinking patterns such as fatty foods, spicy foods, foods with lots of acids, coffee, mint and chocolate which are the culprits. Stay away from bed after eating; wait 2-3 hours and then lie down. Eat smaller meals more often than 2 or 3 large meals. Avoid wearing clothes that are tight in the middle of the body.

Research by de Jong *et al*., showed that providing education can effectively reduce the need for upper gastrointestinal endoscopy in patients with dyspepsia[33]. Non-pharmacological approaches to dyspepsia patients include reassurance, lifestyle modification, psychotherapy, diet, medical food, acupuncture and electrical stimulation [34].

The associated disease or comorbidity is hypertension. A case report study by Nahas et al. [35] found severe hypertension in a 50-year-old male patient with epigastric pain. A report by Fang et al. [36] states that patients infected with Helicobacter pylori have a higher risk of around 1,34 times higher suffering from hypertension than people who are not infected. Hypertension can cause hemodynamic changes related to mucus metabolism. This can be closely associated with a decrease in prostaglandin E2 (PGE2) and an increase in nitric oxide (NO), which causes changes in the thickness of the mucous wall [37]. Other reports show that patients with hypertension factors can worsen patient clinical outcomes compared to those without hypertension [38].

The patient had hypertension and was given amlodipine one tab/24 hours for six days. Strong evidence from a large randomized controlled trial states that amlodipine is effective and safe for reducing cardiovascular events. Amlodipine should be considered a first-line antihypertensive agent [39]. Other reports suggest that amlodipine has proven to be a good drug and is effective in achieving its therapeutic goals at higher rates of patients in special care centres than in primary care and those receiving combination therapy rather than monotherapy [40]. Providing education can improve patient compliance with taking medication and the clinical outcomes of hypertensive patients [41]. Hypertension sufferers can control stress or anxiety about increasing blood pressure. They should not smoke, consume alcohol, and do recreation so that the body and mind become more relaxed and comfortable [42].

Another comorbid disease is hyponatremia. Hyponatremia is an electrolyte disturbance and is associated with significant morbidity and mortality. Hyponatremia conditions can affect health status, causing attention deficit, gait instability, decreased mental function, cerebral oedema, and increased risk of falls, fractures, and osteoporosis [43,44]. Hyponatremia can increase the length of hospital stay by 1-2 days. Hyponatremia conditions are associated with substantial economic and clinical consequences and an increased risk of death [44]. Appropriate and prompt management of hyponatremia helps reduce morbidity and mortality in hyponatremia patients [45]. Administration of 3% NaCl is given to rapidly increase serum sodium concentration because the patient has symptomatic hyponatremia. The cation concentration of the given liquid must exceed the urine cation concentration [46].

The patient's sodium values decreased by 123.1 mmol/L and 130.8 mmol/L. The patient's therapy was NaCl 3% 100 mL/24

hours IV and given for seven days. Giving 3% NaCl required calculation of sodium correction and the amount of 3% NaCl needed. The measure of sodium correction can be seen in Table 1.

In addition, it is necessary to be careful in considering or correcting hyponatremia too quickly can be associated with irreversible brain damage and can cause systemic adverse effects and ageing effects [43]

Table 1. Calculation of sodium correction

Patient's weight = 60 kg	
TBW	= 0,5 x 60 kg ➔ 30 L
Target Na	= 136-146 mmol/L
Corrected Na	= TBW x (Target Na – Patient Na)
	= 30 L x (136 mmo/L – 123,1 mmol/L)
	= 387 mmoL
Content of NaCl 3% 100 mL	
	= 513 mmoL/L (51,3 mmoL/botol)
Amount of 3% NaCl needed	
	= 387 mmoL/513 mmoL
	= 7,54 bottles
	= 7-8 days of therapy

Another comorbid disease is hyperthyroidism. According to Wiersinga et al., [47] state that the global prevalence of hyperthyroidism is 0,2-1,3%. Hyperthyroidism is the overproduction and release of thyroid hormone by the thyroid gland, which causes an inappropriate increase in levels. Hyperthyroidism can affect organ systems such as the cardiovascular, nervous, gastrointestinal and liver [48]. Clinical biochemical tests are needed to ensure hyperthyroid patients such as low TSH, high free thyroxine (FT4) or high free tri-iodothyronine (FT3) [47]. Symptoms of hyperthyroidism include nervousness, anxiety, palpitations, emotional lability, fatigue, weight loss, increased appetite, and heat intolerance. Signs of hyperthyroidism include warm, smooth, moist skin and splendid hair, separation of the nail tip from the nail bed (onycholysis), tachycardia at rest, widened pulse pressure, and a systolic ejection murmur [48]. Thyroid disorders impact the gastrointestinal system [49]. Excess thyroid hormone increases the rate of contractions, and patients often complain of epigastric pain, fullness and erosions. Hyperthyroid patients with gastritis can affect gastric and intestinal motility [50].

The therapy received was methimazole 5 mg/day. Information from the patient's family indicated that the patient had been taking the drug for a long time. According to Wiersinga et al., hyperthyroidism is a common condition with a global prevalence of 0.2-1.3%. Hyperthyroidism is characterized by low TSH, high free thyroxine (FT4) or high free tri-iodothyronine (FT3) [47]. The mechanism of methimazole inhibits the formation of thyroid hormone by interfering with the thyroid peroxidase enzyme, which results in the incorporation of iodine into the thyroglobulin tyrosine residue [51]. Initial methimazole therapy is started with 15 mg/day, and maintenance therapy is 5-10 mg/day for 12-18 months [51,52]. During treatment with methimazole, side effects should be monitored, and every visit should be monitored. Side effects of using methimazole are agranulocytosis (with fever, malaise, gingivitis, oropharyngeal infection and granulocyte count <250/mm3), polymyositis, GI intolerance, hepatotoxicity (Bereda, 2022). Clinical conditions and quality of life should be evaluated. According to Akmal & Kung, monitoring of side effects such as liver function has doubled from average values [53].

CONCLUSION

In Indonesia, patients with functional dyspepsia almost always go to the hospital. Symptoms include feeling full/uncomfortable in the upper abdomen, feeling full quickly,

burning or pain in the epigastrium. Therapy given cliad (clidium/chlordiazepoxide) 1 tab/8 hours, infusion of 3% NaCl 100 mL/24 hours, alprazolam 1 tab/24 hours, injection of pantoprazole 1 amp/24 hours, rebamipide 1 tab/8 hours, amlodipine 1 tab/24 hours, thiazole ½ tab/24 hours, amitriptyline 1 tab/12 and lioresal 10 mg/1 2 hours. Education is provided, such as avoiding and changing eating or drinking patterns such as fatty, spicy foods, foods with lots of acids, and coffee drinks. Don't go to bed right after eating; wait 2-3 hours after eating and then lie down. Eat smaller meals more often than 2 or 3 large meals.

REFERENCES

1. Mahadeva S, Ford AC. Clinical and epidemiological differences in functional dyspepsia between the East and the West. *Neurogastroenterol Motil*. 2016;28(2):167-174. doi:10.1111/nmo.12657
2. Almeida AM, Martins LAG, Cunha PLT, Brasil VW, Félix LGF, Passos M do CF. Prevalence of dyspeptic symptoms and heartburn of adults in Belo Horizonte, Brazil. *Arq Gastroenterol*. 2017;54(1):46-50. doi:10.1590/s0004-2803.2017v54n1-09
3. Hantoro IF, Syam AF. Measurement of Health-related Quality of Life in Patients with Functional Dyspepsia. *Acta Med Indones*. 2018;50(1):88-92.
4. Kim SE, Kim N, Lee JY, et al. Prevalence and Risk Factors of Functional Dyspepsia in Health Check-up Population: A Nationwide Multicenter Prospective Study. *J Neurogastroenterol Motil*. 2018;24(4):603-613. doi:10.5056/jnm18068
5. Kawada T. Epigastric Pain Syndrome, Functional Dyspepsia, and Sleep Disturbance. *Dig Dis Sci*. 2021;66(7):2466-2467. doi:10.1007/s10620-021-07036-9
6. Nishizawa T, Masaoka T, Suzuki H. Functional Dyspepsia: Pathogenesis, Diagnosis, and Treatment. *Journal of General and Family Medicine*. 2016;17(3):204-210. doi:10.14442/jgfm.17.3_204
7. Harmon RC, Peura DA. Review: Evaluation and management of dyspepsia. *Therap Adv Gastroenterol*. 2010;3(2):87-98. doi:10.1177/1756283X09356590
8. Basandra S. Epidemiology of Dyspepsia and Irritable Bowel Syndrome (I BS) in Medical Students of Northern India. *JCDR*. Published online 2014. doi:10.7860/JCDR/2014/10710.5318
9. Lacy BE, Weiser KT, Kennedy AT, Crowell MD, Talley NJ. Functional dyspepsia: the economic impact to patients. *Aliment Pharmacol Ther*. 2013;38(2):170-177. doi:10.1111/apt.12355
10. Grigorian A, Lin MYC, de Virgilio C. Severe Epigastric Pain with Nausea and Vomiting. *Springer Nature*. Published online 2020:228-237. doi:https://doi.org/10.1007/978-3-030-05387-1_20
11. Schellack N, Schellack G, Sandt, N van der, Masuku B. Gastric Pain. *South African Family Practice*. 2015;57(4):13-19.
12. Syam AF, Simadibrata M, Makmun D, et al. National Consensus on Management of Dyspepsia and Helicobacter pylori Infection. *Acta Med Indones*. 2017;49(3):279-287.
13. Oh JH, Kwon JG. Functional Dyspepsia. *Korean J Gastroenterol*. 2019;73(2):77. doi:10.4166/kjg.2019.73.2.77
14. Senay E, Eken C, Yildiz M, et al. Comparison of intravenous pantoprazole and ranitidine in patients with dyspepsia presented to the emergency department: a

randomized, double blind, controlled trial. *World Journal of Emergency Medicine*. 2016;7(1):30. doi:10.5847/wjem.j.1920-8642.2016.01.005

15. Kollins F, Supriatmo S, Saragih R, Ilhamd I. Effectivity of Esomeprazole Compared with Lansoprazole in the Treatment of Pediatric with Gastritis. *Open Access Maced J Med Sci*. 2021;9(B):1424-1427. doi:10.3889/oamjms.2021.7191
16. Khatir IG, Jahanian F, Varedi N, Ahidashti HA, Montazar SH, Hosseininejad SM. Comparison of Intra-Venus Ranitidine with Pantoprazole in Patients with Epigastric Pain Referring to Emergency Department. *app*. 2020;8(1):1-5. doi:10.13189/app.2020.080101
17. Wang WH, Huang JQ, Zheng GF, et al. Effects of Proton-Pump Inhibitors on Functional Dyspepsia: A Meta-analysis of Randomized Placebo-Controlled Trials. *Clinical Gastroenterology and Hepatology*. 2007;5(2):178-185. doi:10.1016/j.cgh.2006.09.012
18. Suzuki H, Okada S, Hibi T. Proton-pump inhibitors for the treatment of functional dyspepsia. *Therap Adv Gastroenterol*. 2011;4(4):219-226. doi:10.1177/1756283X11398735
19. Pinto-Sanchez MI, Yuan Y, Hassan A, Bercik P, Moayyedi P. Proton pump inhibitors for functional dyspepsia. Cochrane Upper GI and Pancreatic Diseases Group, ed. *Cochrane Database of Systematic Reviews*. 2017;2018(3). doi:10.1002/14651858.CD011194.pub3
20. Suyata, Bustami E, Bardiman S, Bakry F. A Comparison of Efficacy between Rebamipide and Omeprazole in the Treatment of NSAIDs Gastropathy. *The Indonesian Journal of Gastroenterology Hepatology and Digestive Endoscopy*. 2004;5(3):89-94.
21. Lee S, Jeong S, Kim W, et al. Rebamipide induces the gastric mucosal protective factor, cyclooxygenase-2, via activation of 5′-AMP-activated protein kinase. *Biochemical and Biophysical Research Communications*. 2017;483(1):449-455. doi:10.1016/j.bbrc.2016.12.123
22. Naito Y, Yoshikawa T. Rebamipide: a gastrointestinal protective drug with pleiotropic activities. *Expert Review of Gastroenterology & Hepatology*. 2010;4(3):261-270. doi:10.1586/egh.10.25
23. Hou D, Yang M, Hu Z, Yang L. Effects of rebamipide for chronic atrophic gastritis: A protocol for systematic review and meta-analysis. *Medicine*. 2020;99(25):e20620. doi:10.1097/MD.0000000000020620
24. Kato T, Araki H, Onogi F, et al. Clinical trial: rebamipide promotes gastric ulcer healing by proton pump inhibitor after endoscopic submucosal dissection—a randomized controlled study. *J Gastroenterol*. 2010;45(3):285-290. doi:10.1007/s00535-009-0157-0
25. Andreev DN, Maev IV, Dicheva DT. Efficiency of the Inclusion of Rebamipide in the Eradication Therapy for Helicobacter pylori Infection: Meta-Analysis of Randomized Controlled Studies. *JCM*. 2019;8(9):1498. doi:10.3390/jcm8091498
26. Takayama M. Efficacy of treatment with rebamipide for endoscopic submucosal dissection-induced ulcers. *WJG*. 2013;19(34):5706. doi:10.3748/wjg.v19.i34.5706
27. El-Zahaby AA, Abdel Alim A, El-Sharawy AF. Role of Rebamipide and \ or Pantoprazole in Preventing Dexamethasone Induced Gastritis in Senile Male Albino Rats. *EJHM*. 2017;67(2):789-805. doi:10.12816/0037837
28. Puasripun S, Thinrungroj N, Pinyopornpanish K, et al. Efficacy and Safety of Clidinium/Chlordiazepoxide as

an Add-on Therapy in Functional Dyspepsia: A Randomized, Controlled, Trial. *J Neurogastroenterol Motil*. 2020;26(2):259-266. doi:10.5056/jnm19186

29. Liu J, Jia L, Jiang S man, Zhou W cong, Liu Y, Xu J. Efects of Low-Dose Amitriptyline on Epigastric Pain Syndrome in Functional Dyspepsia Patients.pdf. *Digestive Diseases and Sciences*. 2021;66:521-525. doi:https://doi.org/10.1007/s10620-020-06191-9
30. Huang W. Effect of amitriptyline on gastrointestinal function and brain-gut peptides: A double-blind trial. *WJG*. 2013;19(26):4214. doi:10.3748/wjg.v19.i26.4214
31. Liu LS, Shenoy M, Pasricha PJ. The analgesic effects of the GABAB receptor agonist, baclofen, in a rodent model of functional dyspepsia: GABAB receptor on gastric hypersensitivity. *Neurogastroenterology & Motility*. 2011;23(4):356-e161. doi:10.1111/j.1365-2982.2010.01649.x
32. Idrus F, Lisal ST, Ganda IJ, Jumiarni. Comparison of Sleep Quality Using Pittsburgh Sleep Quality Index (PSQI) on Patient with Anxiety Disorders Treated Using Long-Term and Short-Term Benzodiazepine Therapy. Published online 2018:7.
33. de Jong JJ, Lantinga MA, Tan ACITL, et al. Web-Based Educational Intervention for Patients With Uninvestigated Dyspepsia Referred for Upper Gastrointestinal Tract Endoscopy: A Randomized Clinical Trial. *JAMA Intern Med*. 2021;181(6):825. doi:10.1001/jamainternmed.2021.1408
34. Wang YP, Herndon CC, Lu CL. Non-pharmacological Approach in the Management of Functional Dyspepsia. *J Neurogastroenterol Motil*. 2020;26(1):6-15. doi:10.5056/jnm19005
35. Nahas R, Pain T, Goulden P. A rare cause of epigastric pain in a middle-aged man. *Case Reports*. 2013;2013(apr25 1):bcr2013009605-bcr2013009605. doi:10.1136/bcr-2013-009605
36. Fang Y, Xie H, Fan C. Association of hypertension with helicobacter pylori: A systematic review and meta-analysis. Karunasagar I, ed. *PLoS ONE*. 2022;17(5):e0268686. doi:10.1371/journal.pone.0268686
37. Simanjuntak LJ, Manan C, Simadibrata M, Gani RA. Pathogenesis in Portal Hypertensive Gastropathy Due to Liver Cirrhosis. *The Indonesian Journal of Gastroenterology Hepatology and Digestive Endoscopy*. 2004;5(3).
38. Handayani F, Bintang AK, Kaelan C. Hubungan Hipertensi, Diabetes Mellitus dan Dislipidemia dengan Luaran Klinis Pasien Iskemik Stroke dengan Hipersomnia. *Jurnal Kesehatan Tadulako*. 2018;4(1):1-6.
39. Fares H, DiNicolantonio JJ, O'Keefe JH, Lavie CJ. Amlodipine in hypertension: a first-line agent with efficacy for improving blood pressure and patient outcomes. *Open Heart*. 2016;3(2):e000473. doi:10.1136/openhrt-2016-000473
40. Valcarcel Y, Jimenez R, Hernandez V, Aristegui R, Gil A. Efficacy and Safety of Amlodipine. *Clin Drug Invest*. Published online 2006:9.
41. Chaerul R, R HU, Anggriani Y, Saragih S. Pengaruh Pelayanan Home Care Apoteker Terhadap Tingkat Kepatuhan, Kepuasan dan Outcome Klinis Pasien Hipertensi di Apotek. *Healthy Tadulako Journal*. 2019;5(3):64. doi:10.22487/j25020749.2019.v5.i3.14059
42. Arifuddin A, Nur AF. Pengaruh Efek Psikologis Terhadap Tekanan Darah

Penderita Hipertensi. *Jurnal Kesehatan Tadulako*. 2018;4(3):48-53.

43. Giuliani C, Peri A. Effects of Hyponatremia on the Brain. *JCM*. 2014;3(4):1163-1177. doi:10.3390/jcm3041163
44. Patterson JH. The Impact of Hyponatremia. *Pharmacotherapy*. 2011;31(5S):5S-8S. doi:10.1592/phco.31.5.5S
45. Edmonds ZV. Pathophysiology, impact, and management of hyponatremia. *Journal of Hospital Medicine*. 2012;7(S4). doi:10.1002/jhm.1932
46. Sahay M, Sahay R. Hyponatremia: A practical approach. *Indian J Endocr Metab*. 2014;18(6):760. doi:10.4103/2230-8210.141320
47. Wiersinga WM, Poppe KG, Effraimidis G. Hyperthyroidism: aetiology, pathogenesis, diagnosis, management, complications, and prognosis. *The Lancet Diabetes & Endocrinology*. 2023;11(4):282-298. doi:https://doi.org/10.1016/S2213-8587(23)00005-0
48. Bereda G. Hyperthyroidism: Definition, Causes, Pathophysiology and Management. *Open Access*. Published online 2022.
49. Kyriacou A, McLaughlin J, Syed AA. Thyroid disorders and gastrointestinal and liver dysfunction: A state of the art review. *European Journal of Internal Medicine*. 2015;26(8):563-571. doi:10.1016/j.ejim.2015.07.017
50. Daher R, Yazbeck T, Jaoude JB, Abboud B. Consequences of dysthyroidism on the digestive tract and viscera. *WJG*. 2009;15(23):2834. doi:10.3748/wjg.15.2834
51. De Leo S, Lee SY, Braverman LE. Hyperthyroidism. *The Lancet*. 2016;388(10047):906-918. doi:10.1016/S0140-6736(16)00278-6
52. Watanabe N, Yoshimura Noh J, Akamizu T, Yamada M, the study group members of the Japan Thyroid Association. Survey of the actual administration of thiamazole for hyperthyroidism in Japan by the Japan Thyroid Association. *Endocr J*. Published online 2021:EJ21-0238. doi:10.1507/endocrj.EJ21-0238
53. Akmal A, Kung J. Propylthiouracil, and methimazole, and carbimazole-related hepatotoxicity. *Expert Opinion on Drug Safety*. 2014;13(10):1397-1406. doi:10.1517/14740338.2014.953796