International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 14, Special Issue 4, 2022

Original Article

COST-EFFECTIVENESS ANALYSIS OF GASTRITIS THERAPY IN AN AIR FORCE HOSPITAL IN BANDUNG, INDONESIA

RIANI TANJUNG[1], YULIA WARDATI[2], DINI NUR AZIZAH[2], BHEKTI PRATIWI[3], RESMI MUSTARICHIE[4], NYI MEKAR SAPTARINI[4*]

[1]Department of Accounting, Vocational School, Universitas Logistik and Bisnis Internasional, West Java, Indonesia, 40151, [2]Department of Pharmacy, Faculty of Mathematic and Natural Sciences, Al Ghifari University, West Java, Indonesia, 40293, [3]School of Pharmacy, Bandung Institute of Technology, West Java, Indonesia, 40116, [4]Department of Pharmaceutical Analysis and Medicinal Chemistry, Faculty of Pharmacy, Universitas Padjadjaran, West Java, Indonesia, 45363
Email: nyi.mekar@unpad.ac.id

Received: 14 Jul 2022, Revised and Accepted: 20 Aug 2022

ABSTRACT

Objective: This study aimed to analyze the cost-effectiveness of gastritis treatment and the influence factors of cost-effectiveness at an air force hospital in Bandung, West Java, Indonesia.

Methods: Data were collected retrospectively from patient medical records and Hospital Information System (HIS). This study was conducted from August to October 2020. Cost data includes total costs from the perspective of the hospital (health care) and the perspective of the Social Security Administrator for Health (Badan Penyelenggara Jaminan Sosial, BPJS, payer) based on Indonesian-Case Based Groups rates. Outcomes in this study were length of stay (LOS) and leukocytes.

Results: There were 129 patients in inpatient units in the year of 2018-2019. The medicines for gastritis therapy were omeprazole and ranitidine injection and lansoprazole and ulsidex tablet. The most cost-effective therapy based on LOS was ranitidine injection, while based on reducing leukocytes was, ranitidine injection from the payer's perspective and lansoprazole from healthcare perspective.

Conclusion: There was no significant cost difference between the four treatment options. The sensitivity test showed that the influence factor of the Incremental Cost Effectiveness Ratio (ICER) value was decreased leukocytes.

Keywords: LOS, Leukocytes, Medicine, Pharmacoeconomic, Sensitivity test

DOI: https://dx.doi.org/10.22159/ijap.2022.v14s4.PP06 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Gastritis defines any inflammation of the gastric mucosa, including erosive state to the stomach lining tissue, which may occur in acute or chronic state [1]. The exposure of the gastric mucosa to harmful factors and its resistance to automatic digestion by gastric secretions is due to the mucous gel layer that coats the inner surface and acts as a tissue protector [2]. The gastritis prevalence in Indonesia reached 274,396 cases out of 238,452,952 inhabitants. In West Java Province, the gastritis prevalence reached 31.2% and 15.73% in Bandung city [3].

Common causes of acute gastritis are alcohol, long intake od non-steroidal anti-inflammatory drugs (NSAIDs), aspirin for rheumatoid and osteoarthritis patients [4]. While chronic gastritis caused by stress, chronic bile reflux, autoimmune disorders, and *Helicobacter pylori* infection. The observed symptoms are nausea, vomiting, indigestion, burning sensation, and abdominal bloating [6]. Gastritis therapies are H_2 receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs). H_2RAs, such as cimetidine, ranitidine, or famotidine are given when antacids are not enough to relieve gastritis symptoms. If H_2RA is considered less able to reduce gastric acid secretion, PPIs can be given, like omeprazole, lansoprazole, and esomeprazole. PPIs are used for chronic gastritis or has a moderate to severe severity, while antacids and H_2RA are used for mild gastritis [7]. Gastritis treatment uses different types of drugs with different mechanisms of action and costs, so it was necessary to conduct a pharmacoeconomic assessment.

Pharmacoeconomic study using the cost-effectiveness analysis (CEA) method was conducted to control cost-effectiveness [7]. CEA is done by calculating the ratio between the total costs (costs) incurred with the results of therapy (outcomes). This study aimed to analyze the cost-effectiveness of gastritis treatment and the influence factors of cost-effectiveness at an air force hospital in Bandung, West Java, Indonesia in 2018-2019. The results of this study need to be published to provide an explanation of the effectiveness of treatment based on CEA. This study needs to be done because of high prevalence of gastritis, i.e. more than 15% in the Bandung city, Indonesia, so it was necessary to calculate CEA to help drugs selection to reach the optimal health outcome.

MATERIALS AND METHODS

Subjects

The study was approved by the Health Research Ethics Committee of Dr. Hasan Sadikin Hospital, Indonesia, No. LB.04.03/A05/EC/095. III/2021. This study was conducted accordingly to an approved method.

Determination of drug pattern

The drug pattern use in gastritis patients in inpatient units was collected from drug data in the Hospital Information System (HIS). The steps were data collection from HIS, then the medicines for this study was determined according to gastritis therapy.

Determination of alternative criteria

Alternative criteria were gastritis patients in inpatient units who receive gastritis therapy based on medical record and HIS. The steps of data selection were selected medical record based on age category and adjusted to HIS data, then alternative criteria were determined for gastritis patients who have been selected according to age category.

Determination of population criteria

This study was conducted retrospectively based on the medical record, drug, and administrative data [8, 9]. Inclusion criteria include (a) Social Security Administrator for Health (SSAH or BPJS, Badan Penyelenggara Jaminan Sosial) gastritis patients who were treated in the Inpatient Unit in 2018-2019, (b) Gastritis patients aged 26-45 y, (c) The medical record with a gastritis history of using drug therapy for gastritis, and (d) Gastritis patients with complicated and uncomplicated diseases. While, exclusion criteria include (a) Incomplete, missing, or illegible patient

status, (b) Gastritis patients who are forced home or die, and (c) Gastritis patients without gastritis therapy.

Determination of outcome

The outcome was the effectiveness of gastritis patients in the Inpatient Unit by comparing the prescribed drug, which was diagnosed as cured by the doctor based on the length of stay (LOS) and the decreased leukocytes.

Determination of perspective

The perspective was the perspective of the hospital (healthcare) and BPJS (payer) [8, 9].

Determination of cost component

The cost components based on the healthcare perspective were costs for registration, emergency room, room and doctor, nursing care, gastritis drug, medical devices, and other drugs than gastritis drugs. While based on the payer perspective in accordance with the rates of Indonesian-Case Based Groups (INA-CBG's) were collected from administrative data and hospital claim units. Costs were expressed in Indonesian rupiah (IDR) [8, 9].

Study design

The preliminary study was literature research to determine (a) total population of gastritis patients based on inclusion and exclusion criteria, and (b) assessing the gastritis prevalence in the Inpatient Unit in 2018-2019. Data resources were medical records of gastritis patients in inpatient unit, prescribed drug from HIS, and the list of therapy costs from the finance department.

Data analysis

Data analysis begin with the subject characteristics were age, gender, financial guarantee, inpatient class, number of comorbidities, and LOS. Then, cost and effectiveness parameters include cost of registration, emergency room, room and doctor, nursing care, gastritis drug, medical device, and other drugs, were determined. While, the details of costs incurred for BPJS patients were based on Indonesian-Case Based Groups (INA-CBG's) rates. The p-value was determined to assess the data normality. While the statistical analysis was conducted to determine the difference in the total cost of the effectiveness difference. Cost-effectiveness Analysis (CEA) was conducted by calculating the ratio between the total costs (costs) with the results of therapy (outcomes). Data analysis was carried out by calculating the Cost Effectiveness Ratio (COR). The best cost-effectiveness was easier to conclude by made cost-effectiveness tables and diagrams. Then, the Incremental Cost Effectiveness Ratio (ICER) was calculated. The last step was the sensitivity test, which was conducted to determine the cost parameters that affect the ICER value.

RESULTS

Table 1: Drug pattern in air force hospital

Type of drug	Dosage
Omeprazole injection	40 mg, once a day, i. v. 20-30 min
Ranitidine injection	50 mg, once a day, i. v.
Lansoprazole tablet	30 mg, twice a day, 1 h before meal
Ulsidex tablet	500 mg, three times a day, 1 h before meal

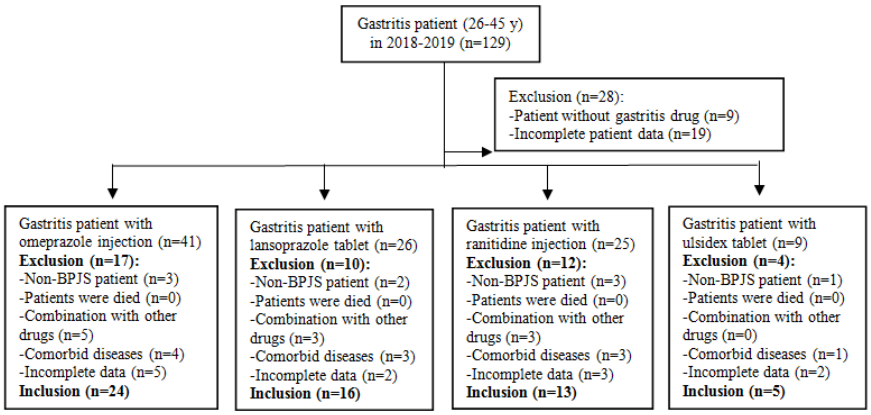

Fig. 1: Patient data collection based on inclusion and exclusion criteria in adult patients

Table 2: Characteristics of subjects

Characteristics	Omeprazole (n=24)	Lansoprazole (n=16)	Ranitidine (n=13)	Ulsidex (n=5)	Total (n=58)	p-value
Age (years)						
26-35	12 (50)	7 (43.8)	7 (53.8)	3 (60.0)	29 (50.0)	0.200
36-45	12 (50.0)	9 (56.2)	6 (46.2)	2 (40.0)	29 (50.0)	
Gender						
Female	15 (62.5)	12 (75.0)	8 (61.5)	3 (60.0)	38 (65.5)	0.200
Male	9 (37.5)	4 (25.0)	5 (38.5)	2 (40.0)	20 (34.5)	
Financing guarantee						
BPJS non-PBI	18 (75.0)	11 (68.8)	10 (76.9)	4 (80.0)	43 (74.1)	0.135
BPJS PBI	6 (25.0)	5 (31.2)	3 (23.1)	1 (20.0)	15 (25.9)	
type of inpatient room						
Class I	5 (20.8)	3 (18.7)	1 (7.7)	1 (20.0)	10 (17.2)	0.002*
Class II	5 (20.8)	3 (18.8)	3 (23.1)	0 (0)	15 (25.9)	
Class III	14 (58.4)	10 (62.5)	9 (69.2)	4 (80.0)	33 (56.9)	
Number of comorbid						
0-2	19 (79.2)	13 (81.2)	10 (76.9)	4 (80.0)	46 (79.3)	0.028
>2	5 (20.8)	3 (18.8)	2 (23.1)	1 (20.0)	12 (20.7)	
LOS (days)						
1-3	14 (58.3)	4 (25.0)	9 (69.2)	1 (20.0)	28 (48.3)	0.002
4-7	10 (41.7)	12 (75.0)	4 (30.8)	4 (80.0)	30 (51.7)	

PBI is Penerima Bantuan Iuran or Contribution Assistance recipient (CAR), *p<0.05 mean data was significantly different

Table 3: Parameter of cost and outcome

	Omeprazole (n=24)	Lansoprazole (n=16)	Ranitidine (n=13)	Ulsidex (n=5)	p-value
Parameter of cost (IDR)					
Registration	25,000	25,000	25,000	25,000	-
Emergency room	75,000	75,000	75,000	75,000	-
Room and doctor	958,958	1,101,563	839,038	1,061,000	0.684
Nursing care	175,000	206,250	173,033	220,000	0.274
Gastritis drug	46,568	6,980	5,265	5,848	0.004*
Medical devices and other	350,000	412,500	346,154	440,000	0.272
drugs than gastritis drugs	1,630,526	1,827,293	1,463,490	1,826,848	0.278
Health care total cost	2,533,600	2,505,450	2,425,331	2,432,262	0.284
Payer total cost					
Parameter of outcome					
LOS (days)	3.5±1.2	4.1±1.3	3.5±1.4	4.4±0.9	0.224
Decreased leukocytes (cell/mm^3)	3.800	3.500	3.300	3.100	0.276

*p<0.05 mean data was significantly different

Table 4: CER ratio and ICER on LOS

Group	Total cost (IDR)		LOS (days)	CER (IDR/day)		ICER (IDR)	
	Payer	Health care		Payer	Health care	Payer	Health care
Omeprazole	2,533,600	1,630,526	3.5±1.2	723,886	465,865	O-L 46,917 O-U 112,598	-
Lansoprazole	2,505,450	1,827,293	4.1±1.3	611,085	445,681	L-O 46,917 L-U 243,960	L-U 1,483
Ranitidine	2,425,331	1,463,490	3.5±1.4	692,952	418,140	-	-
Ulsidex	2,432,262	1,826,848	4.4±0.9	552,787	415,193	U-L 243,960 U-O 112.598	U-L 1,483

L= Lansoprazole Tablet, O= Omeprazole Injection, R= Ranitidine Injection, U= Ulsidex Tablet

Table 5: Cost-effectiveness (payer) on LOS effectiveness

Cost-effectiveness	Lower cost	Same cost	Higher cost
Lower effectiveness	A L-O, U-L U-O	B	C L-R U-R
Same effectiveness	D R-O	E	F O-R
Higher effectiveness	G R-L R-U	H	I O-L, L-U O-U

L= Lansoprazole Tablet, O= Omeprazole Injection, R= Ranitidine Injection, U= Ulsidex Tablet

Table 6: Cost-effectiveness (health care) on LOS effectiveness

Cost-effectiveness	Lower cost	Same cost	Higher cost
Lower effectiveness	A U-L	B	C L-O, U-O L-R, U-R
Same effectiveness	D R-O	E	F O-R
Higher effectiveness	G O-L, R-L O-U, R-U	H	I L-U

L= Lansoprazole Tablet, O= Omeprazole Injection, R= Ranitidine Injection, U= Ulsidex Tablet

Table 7: CER and ICER on decreased leukocytes

Group	Total cost (IDR)		Decreased leukocytes (cell/mm3)	CER (IDR/day)		ICER (IDR)	
	Payer	Health care		Payer	Health care	Payer	Health care
Omeprazole	2,612,420	2,221,534	3,800	687	585	O-L 450 O-R 495 O-U 193	O-L 523 O-R 203 O-U 315
Lansoprazole	2,477,300	2,064,704	3,500	708	590	L-O 450 L-R 563	L-O 523 L-U 160
Ranitidine	2,364,700	2,119,860	3,300	717	642	R-L 563 R-O 495	R-O 203 R-U 596
Ulsidex	2,477,300	2,000,688	3,100	799	645	U-O 193	U-L 160 U-R 596 U-O 315

Table 8: Cost-effectiveness (payer) on leukocytes effectiveness

Cost-effectiveness	Lower cost	Same cost	Higher cost
Lower effectiveness	A	B	C
	L-O, R-L	U-L	U-R
	R-O, U-O		
Same effectiveness	D	E	F
Higher effectiveness	G	H	I
	R-U	L-U	O-L, O-U
			O-R, L-R

Table 9: Cost-effectiveness (Health Care) on leukocytes effectiveness

Cost-effectiveness	Lower cost	Same cost	Higher cost
Lower effectiveness	A	B	C
	L-O, U-L		R-L
	R-O, U-R, U-O		
Same effectiveness	D	E	F
Higher effectiveness	G	H	I
	L-R		O-L, L-U
			O-R, R-U, O-U

Table 10: Sensitivity test on leukocyte effectiveness (ulsidex-lansoprazole)

Parameter	Lower limit	Upper limit	Difference
Decreased leukocytes	213	135	78
Doctor and room cost	121	189	68
Gastritis drug cost	159	161	2

DISCUSSION

Gastritis drugs to gastritis patients in the inpatient unit were omeprazole and lansoprazole injection and lansoprazole and ulsidex tablets (table 1). The pattern of gastritis drugs of Air Force Hospital based on hospital formulary. Omeprazole and lansoprazole are PPIs. PPIs are the most potent suppressors of gastric acid secretion available and are widely used in the treatment of gastroesophageal reflux and peptic ulcer disease. PPIs are prodrugs that require gastric acid for activation [10]. PPIs are the most effective therapy for the full spectrum of acid reflux-related diseases [11]. PPIs are also recommended to decreased gastric acid production and facilitate quick healing [12]. Ulsidex tablets contain sucralfate, which is a base of aluminum saccharose sulfate, which on the surface of the ulcer will form a complex compound with protein, which will prevent the attack of aggressive factors, such as hydrochloric acid, pepsin, and bile. Ranitidine is an H_2RA, which competitively block the histamine H_2 receptor, inhibiting basal acid secretion and acid secretion stimulated by histamine [13].

Gastritis patients in the inpatient unit in 2018-2019 were 258 patients. Patients were divided into three groups, i.e. adolescents (12-25 y) of 72 patients, adults (26-45 y) of 129 patients, and the elderly (46-65 y) of 57 patients. In this study, there were no patients who received a combination of the four gastritis drugs. This was because drugs with the same mechanism of action were not given simultaneously. This study for CEA only focused on adults due to the most patients. This result was in accordance with Du *et al.*, in which the most patients were in the 18-65 y [14]. Fig. 1 showed the flow of data collection carried out according to the inclusion and exclusion criteria. Gastritis mostly affects adults due to productive age, which work activities affect the physical pressure on the digestive system. The other factors that affect the prevalence gastritis in adults were irregular eating patterns, stress at work, smoking habits, obesity, and other unhealthy lifestyles [15].

Table 2 showed that gastritis often occurs in female (62.5%), because the stress level in female is higher than in male. Female more difficult to control emotions which trigger stress, as one of the factors that cause gastritis. Psychologically, female use feelings and emotions more than male, so vulnerable to experience psychological stress [16]. Table 2 showed that none of the various characteristics differed significantly, except the type of inpatient room and the number of comorbids ($p<0.05$) [17]. Most patients were female, which accordance with South Korea result, i.e. ratio of 89:101 [18].

Direct medical costs are costs that are directly related to health care. The calculation of direct medical costs has three components, i.e. medical, maintenance, and laboratory costs [19]. Table 3 showed that the cost and outcome components were not significantly different ($p>0.05$), except for gastritis drugs. The injectable preparations (omeprazole and ranitidine) gave shorter LOS than oral preparations (lansoprazole and ulsidex). Intravenous injection preparations, without a biopharmaceutical stage, gave faster treatment than oral preparations [20]. Omeprazole injection gave the highest decreased leukocytes, due to the route of administration. While, ranitidine injection similar to tablet preparations. This was assumed that gastritis was caused by psychological and not caused by infection [5]. The limitations in this study were the selected subjects based on medical records, so there was potential for selection bias and the limited number of subjects. So, that more subjects were needed to determine the cause of gastritis more precisely. According to guidelines, ranitidine is the second line, while lansoprazole and omeprazole are the third line [6]. So, by increasing the number of patients, it is hoped that the results will be clearer, whether the results of this study were the same or not for different populations. If after increasing the number of patients, the results were the same, then it is necessary to further investigate the causative factors, such as anatomical and physiological factors in the area or clinical pharmacy factors. If there were no problems with these factors, then the health outcome may be due to drug factors.

Table 4 showed that ranitidine and omeprazole were effective at improving gastritis; however, ranitidine provided lower cost for payer and health care. This result was in accordance with Kaplan-Machlis *et al.*, who reported that more omeprazole-treated patients reported improved heartburn resolution compared with ranitidine-treated patients in West Virginia, USA [21]. Omeprazole is a PPI, which the most effective therapy for the full spectrum of acid reflux-related diseases [11]. While, ranitidine is an H_2RA, which competitively block the histamine H_2 receptor [13]. This causes therapy with omeprazole give a better outcome than ranitidine.

In table 5 and 6, there were L-O, U-O, L-R, ect, which means the two drugs were compared regarding cost-effectiveness and LOS-effectiveness. In table 5, drug dominance was observed from

ranitidine to lansoprazole and ulsidex, lansoprazole and ulsidex to omeprazole, and ulsidex to lansoprazole, so ICER calculations were required. In table 6, drug dominance was observed from omeprazole and ranitidine to lansoprazole and ulsidex, ulsidex to lansoprazole, so the calculation of ICER was required. Ranitidine was more cost-effective than omeprazole. Table 5 and 6 showed that ranitidine was the best drug compared the other gastritis drug to gastritis patients at the inpatient unit. Column A and I in table 5 and 6 showed that there were need ICER calculation to determine which better CEA, whereas column C was rejected as CEA. Table 5 showed that lansoprazole has lower cost-and LOS-effectiveness than omeprazole, to make the drug selection, it is necessary to calculate ICER.

Increased leukocytes due to systemic inflammation is an infection response induced by the secretion of proinflammatory cytokines [22]. So, it was important to measure the decrease in leukocytes to determine the efficacy of gastritis therapy with gastritis drugs. Table 7 showed that omeprazole was the most effective in decreased leukocytes at improving gastritis compare to other drugs. This result was accordance with Fasseas *et al.* [23] and Hofbauer *et al.* [24]. This was due to the inhibitory effect of omeprazole on leukocyte transmigration through endothelial cell monolayers and leukocyte adhesion [24], resulting in low leukocyte levels when the patient was treated with omeprazole.

Table 8 and 9 showed that ranitidine (payer's perspective) and lansoprazole (health care's perspective) was the most cost-effective therapy the based on decreased leukocytes. Based on pharmacokinetic data, lansoprazole-based therapy may be a better alternative than omeprazole-based therapy. Column A and I in table 8 and 9 showed that there were need ICER calculation to determine which better CEA, whereas column C was rejected as CEA. This study was aimed to compare the effectiveness of a triple therapy regimen with omeprazole or lansoprazole in eradicating *H. pylori* infection [25]. Switching from ranitidine to omeprazole will result in cost savings, thus becoming cost-effective [26].

After ICER calculating, a sensitivity test was calculated in table 10 to determine the cost parameters that affect the ICER. The sensitivity test value was determined from the difference between the lower and the upper limit value, i.e. ICER±25%. The highest value was the most influence parameter on the ICER value [27,28], i. e decreased leukocytes. The application of this study was to determine the best health outcome based on CEA. The results showed that there was no significant difference between the four drug patterns in Air Force Hospital.

CONCLUSION

There was no significant cost difference between the four treatment options. The sensitivity test showed that the influence factor of the ICER value was decreased leukocytes.

FUNDING

Nil

AUTHORS CONTRIBUTION

All the authors contributed equally.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Dore MP, Graham DY. Ulcers and gastritis. Endoscopy. 2010;42(1):38-41. doi: 10.1055/s-0029-1215314, PMID 19904699.
2. Szabo S, Trier JS, Frankel PW. Sulfhydryl compounds may mediate gastric cytoprotection. Science. 1981;214(4517):200-2. doi: 10.1126/science.7280691, PMID 7280691.
3. The Ministry of Health of the Republic of Indonesia. Center for data and information on non-communicable diseases, Jakarta: Ministry of Health of the Republic of Indonesia; 2012.
4. Fauci AS, Kasper DL, Longo DL, Braunwald E, Hauser SL, Jameson JL. 17th ed. Harrison's Intern Med. 2008;38(12):932-46.
5. Andersen LP. Colonization and infection by Helicobacter pylori in humans. Helicobacter. 2007;12Suppl 2:12-5. doi: 10.1111/j.1523-5378.2007.00574.x, PMID 17991171.
6. Wells BG, Dipiro J, Schwinghammer TL, DiPiro CV. Pharmacotherapy handbook. 9th ed. New York: McGraw-Hill Companies, Inc; 2015.
7. Grosse SD. Assessing cost-effectiveness in health care: the history of the $50,000 per QALY threshold. Value Health. 2008;8:165-78.
8. Tanjung R, Wardati Y, Saptarini NM. Cost-effectiveness analysis of typhoid fever inpatient in the private hospital in Subang, Indonesia. Drug Invent Today. 2020;14(2):344-7.
9. Tanjung R, Wardati Y, Saptarini NM. Cost-effectiveness analysis of prolanis of type 2 diabetic patients in three community health centers in Bandung, Indonesia. Int J Appl Pharm. 2021;13Special Issue 3:28-31.
10. Liver Tox. Clinical and research information on drug-induced liver injury. Bethesda: National Institute of Diabetes and Digestive and Kidney Diseases. Proton Pump Inhibitors. 2012. PMID 31643228.
11. Malfertheiner P, Kandulski A, Venerito M. Proton-pump inhibitors: understanding the complications and risks. Nat Rev Gastroenterol Hepatol. 2017;14(12):697-710. doi: 10.1038/nrgastro.2017.117, PMID 28930292.
12. Sakamoto Y, Shimoyama T, Nakagawa S, Mikami T, Fukuda S. Proton pump inhibitor treatment decreases the incidence of upper gastrointestinal disorders in elderly Japanese patients treated with NSAIDs. Intern Med. 2014;53(11):1107-11. doi: 10.2169/internal medicine.53.2159, PMID 24881732.
13. France MM, Turner JR. The mucosal barrier at a glance. J Cell Sci. 2017;130(2):307-14. doi: 10.1242/jcs.193482, PMID 28062847.
14. Du Y, Bai Y, Xie P, Fang J, Wang X, Hou X. Chronic gastritis in China: a national multi-center survey. BMC Gastroenterol. 2014;14(14):21. doi: 10.1186/1471-230X-14-21, PMID 24502423.
15. Vincent K. Gastritis and peptic ulcer disease. In: Kellerman R, Rakel D, editors. Conn's current therapy. Amsterdam, Netherlands: Elsevier; 2021. p. 210-13.
16. Agarwal A, Gupta S, Sharma RK. Role of oxidative stress in female reproduction. Reprod Biol Endocrinol. 2005;3:28. doi: 10.1186/1477-7827-3-28, PMID 16018814.
17. Schfler WC. Statistics for biology, pharmacy, medicine and related sciences. Bandung, Indonesia: ITB Publisher; 1987.
18. Chang YW, Ko WJ, Oh CH, Park YM, Oh SJ, Moon JR. Clarithromycin resistance and female gender affect Helicobacter pylori eradication failure in chronic gastritis. Korean J Intern Med. 2019;34(5):1022-9. doi: 10.3904/kjim.2018.054, PMID 29898576.
19. Regulation of the Minister of Health of the Republic of Indonesia. Vol. 69 of. Jakarta, Indonesia: Basic Book Company Health Research; 2013. p. 2013.
20. Jin JF, Zhu LL, Chen M, Xu HM, Wang HF, Feng XQ. The optimal choice of medication administration route regarding intravenous, intramuscular, and subcutaneous injection. Patient Prefer Adherence. 2015;9:923-42. doi: 10.2147/PPA.S87271, PMID 26170642.
21. Kaplan Machlis B, Spiegler GE, Zodet MW, Revicki DA. Effectiveness and costs of omeprazole vs ranitidine for treatment of symptomatic gastroesophageal reflux disease in primary care clinics in West Virginia. Arch Fam Med. 2000;9(7):624-30. doi: 10.1001/archfami.9.7.624, PMID 10910310.
22. Pece S, Giuliani G, DiLeo A, Fumarola D, Antonaci S, Jirillo E. Role of lipopolysaccharide and related cytokines in helicobacter pylori infection. Recent Prog Med. 1997;88:237-41.
23. Fasseas P, Leybishkis B, Rocca G. Omeprazole versus ranitidine in the medical treatment of acute upper gastrointestinal bleeding: assessment by early repeat endoscopy. Int J Clin Pract. 2001;55(10):661-4. PMID 11777288.
24. Hofbauer R, Losert H, Gmeiner B, Wagner O, Kapiotis S, Frass M. Inhibitory effect of omeprazole on transmigration of leukocytes through endothelial cell monolayers and leukocyte adhesion. Microvasc Res. 2000;59(1):169-71. doi: 10.1006/mvre.1999.2196, PMID 10625584.

25. Niv Y. Effectiveness of omeprazole-versus lansoprazole-based triple therapy for Helicobacter pylori eradication. Dig Dis Sci. 2005;50(5):839-41. doi: 10.1007/s10620-005-2649-y, PMID 15906754.
26. Stalhammar NO, Carlsson J, Peacock R, Muller Lissner S, Bigard MA, Porro GB. Cost effectiveness of omeprazole and ranitidine in intermittent treatment of symptomatic gastro-oesophageal reflux disease. Pharmacoeconomics. 1999;16(5 Pt 1):483-97. doi: 10.2165/00019053-199916050-00006, PMID 10662395.
27. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddant GL. Methods for the economic evaluation of health care programmes. UK: Oxford University Press; 2005.
28. Gray AM, Clarke PM, Wolstenholme JL, Wordsworth S. Applied methods of cost effectiveness analysis in health care. UK: Oxford University Press; 2011.