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Post-Prescription Review and Feedback: A Major Specialist Hospital Experience

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Abstract

Introduction: One of the key Antimicrobial stewardship (AMS) interventions is post-prescription review and feedback (PPRF), which allows clinicians to initiate empirical antibiotic regimens based on clinical judgment while facilitating the AMS team review to guide therapy adjustments.

Objective: This study aimed to describe the implementation of an intensified PPRF in a major specialist hospital and compare the antibiotic consumption before and after the intervention.

Methods: An observational study was conducted at a major specialist hospital in Sabah, Malaysia, from July to December 2019. Data on patient demographic information, the type and indication of antibiotics prescribed, and the interventions made by the AMS team were collected. Data on the antibiotic consumption was extracted from the hospital's in-house electronic database. Antibiotic usage data from the pre-intervention period (July to December 2018) was compared with the post-intervention period (July to December 2019), during which an intensified PPRF approach was applied.

Results: A total of 538 patients who received antibiotics were included in the study, and 847 PPRF reviews were conducted during the six-month post-intervention period. On average, the AMS team performed reviews on an average of 2.5 ± 2.3 days after the primary team initiated antibiotic therapy. The overall antibiotic consumption decreased significantly by 56.31% (316.23 to 138.15 DDD/1,000 patient days) after the intervention ($p<0.001$).

Conclusion: The intensified PPRF strategy, supported by a dedicated AMS team and alongside other AMS strategies, may help to reduce antibiotic usage. Further studies are warranted to explore the effects of PPRF on patient outcomes and antimicrobial resistance patterns.

Keywords: Antimicrobial stewardship, prescription review, hospital, antibiotic, feedback

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Introduction

In recent years, antimicrobial resistance (AMR) has emerged as a significant global health concern, posing threats to individual health and imposing escalating costs on healthcare systems worldwide (1–4). Effective and urgent measures to control AMR are crucial to mitigating this growing crisis. In Malaysia, rising resistance rates against pathogens such as methicillin-resistant Staphylococcus aureus (MRSA), carbapenem-resistant Acinetobacter baumannii (CRAB), and extended-spectrum beta-lactamase (ESBL)-producing Klebsiella pneumoniae have been reported (5). Overutilisation of antimicrobials is a major driver of AMR, contributing to the increasing prevalence of resistant organisms (6–8).

Antimicrobial Stewardship Programme (AMS) was introduced to promote prudent antimicrobial use in healthcare settings. The programme had demonstrated positive impacts on lowering antibiotic utilisation, improving patient outcomes, and reducing adverse effects such as *Clostridium difficile* infections and subsequently reducing the development of antibiotic resistance (10–13). The second edition of the "Protocol on AMS Programme in Healthcare Facilities," published by the Ministry of Health Malaysia's Pharmaceutical Services Program in 2022, listed prospective audit and feedback (PAF) as one of the core strategies for the implementation of AMS in hospitals, alongside other strategies such as antimicrobial consumption

surveillance and feedback mechanism, formulary restriction, pre-authorisation, antimicrobial order tools, de-escalation, and antimicrobial rounds by AMS team (14). The 2016 guidelines by the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) recommended PAF as one of the key AMS strategies (15). Post-prescription review and feedback (PPRF) is a type of PAF that allows clinicians to initiate empirical antibiotic regimens based on clinical judgment while enabling the AMS team to review and provide recommendations for continuing, adjusting, or discontinuing therapy based on patient-specific factors (16). During patient reviews, the AMS team also communicate with the primary team on the antibiotic appropriateness, with the goal of improving future antibiotic utilisation.

In 2018, the National Surveillance on Antibiotic Utilisation (NSAU) identified Hospital Queen Elizabeth II (HQE II) as one of the top three users of broad-spectrum antibiotics, including cephalosporins, carbapenems, and piperacillin-tazobactam, among major specialist hospitals in Malaysia (9). This concerning findings spurred efforts to intensify the strategies aimed at reducing antimicrobial consumption. At HQE II, the AMS programme was established in 2017 with weekly AMS rounds held on Thursdays, focusing on patients receiving broad-spectrum antibiotics such as carbapenems, piperacillin-tazobactam, ceftazidime, cefepime, vancomycin, and polymyxin E, and providing feedback to guide the continuation, modification, or discontinuation of antibiotic therapy based on patient-specific factors and evolving clinical data. The AMS team comprises an infectious disease specialist, rotational doctors from the general medical and microbiology departments, and two clinical pharmacists. Despite these efforts, HQE II continued to report high antibiotic usage, particularly for cefuroxime and ceftriaxone, which surpassed the national upper limit. Both cefuroxime and ceftriaxone were not initially included in the PPRF reviews. Although cefuroxime and ceftriaxone are classified as narrow-spectrum antibiotics, their overuse is associated with the induction of ESBL production, and this is a serious concern in the context of AMR (17). To address this, a more intensified PPRF strategy was introduced in the year of 2019, increasing the frequency of AMS rounds to twice weekly and expanding the PPRF review to include cefuroxime and ceftriaxone.

The efficacy of PAF and PPRF strategies has been extensively documented in the literature (16, 18, 19) but most studies were conducted in the Western countries. There was limited data on the impact of these AMS strategies on antibiotic consumption and AMR in the local setting. Therefore, this study aimed to describe the implementation of PPRF at HQE II and to compare the antibiotic usage during the pre-intervention period (July to December 2018) with the post-intervention period (July to December 2019). The findings from this study were intended to highlight the potential impact of PPRF and encourage more policies that help to optimise antibiotic use and combat antibiotic resistance.

Method

This observational study was conducted at Hospital Queen Elizabeth II (HQE II), Sabah, Malaysia, from July 2019 to December 2019. HQE II is a major specialist hospital with 300 beds and seven clinical departments. This study was registered with the National Medical Research Registry (NMRR-20-676-54434) and received approval from the Medical Research and Ethics Committee (MREC) of the Ministry of Health Malaysia.

All patients prescribed with the targeted antibiotics reviewed by the AMS team during July 2019 to December 2019 were included in the study. Exclusion criteria for the study included patients under 18 years of age, those receiving care in the emergency department during the review day, and patients receiving antibiotics not listed in the study or administered via non-parenteral routes. A standardised data collection form was used to extract relevant information, including patient demographics, the type and indication of antibiotic use, and the interventions recommended by the AMS team. In this study, the in-house electronic database (Pharmacy Information System, PhIS) was used to identify patients who received broad spectrum antibiotics as well as to retrieve data on antibiotic consumption. Information on patient demographics, antibiotic indication and AMS intervention were captured from the AMS registry (in the form of google sheet). Antibiotic consumption data were collected for both the post-intervention period (the study period) and the pre-intervention period in 2018 (July to December 2018).

Post-prescription Review and Feedback (PPRF) Workflow and Intervention

The PPRF process was outlined in Figure 1. The study included all adult patients admitted to the wards (medical, surgical, orthopaedic and intensive care) who were prescribed with the targeted intravenous antibiotics by the primary treatment team. The AMS pharmacist identified eligible patients using the hospital's in-house electronic database on the day before every AMS round. The targeted intravenous

antibiotics included second-generation cephalosporins and above (cefuroxime, ceftriaxone, ceftazidime, cefotaxime, cefoperazone-sulbactam, cefepime, ceftaroline), fluoroquinolones (ciprofloxacin), carbapenems (meropenem, imipenem, ertapenem), glycopeptides (vancomycin), oxazolidinones (linezolid), broad-spectrum beta-lactam/beta-lactamase inhibitors (piperacillin-tazobactam), and polymyxin-based antibiotics (colistin).

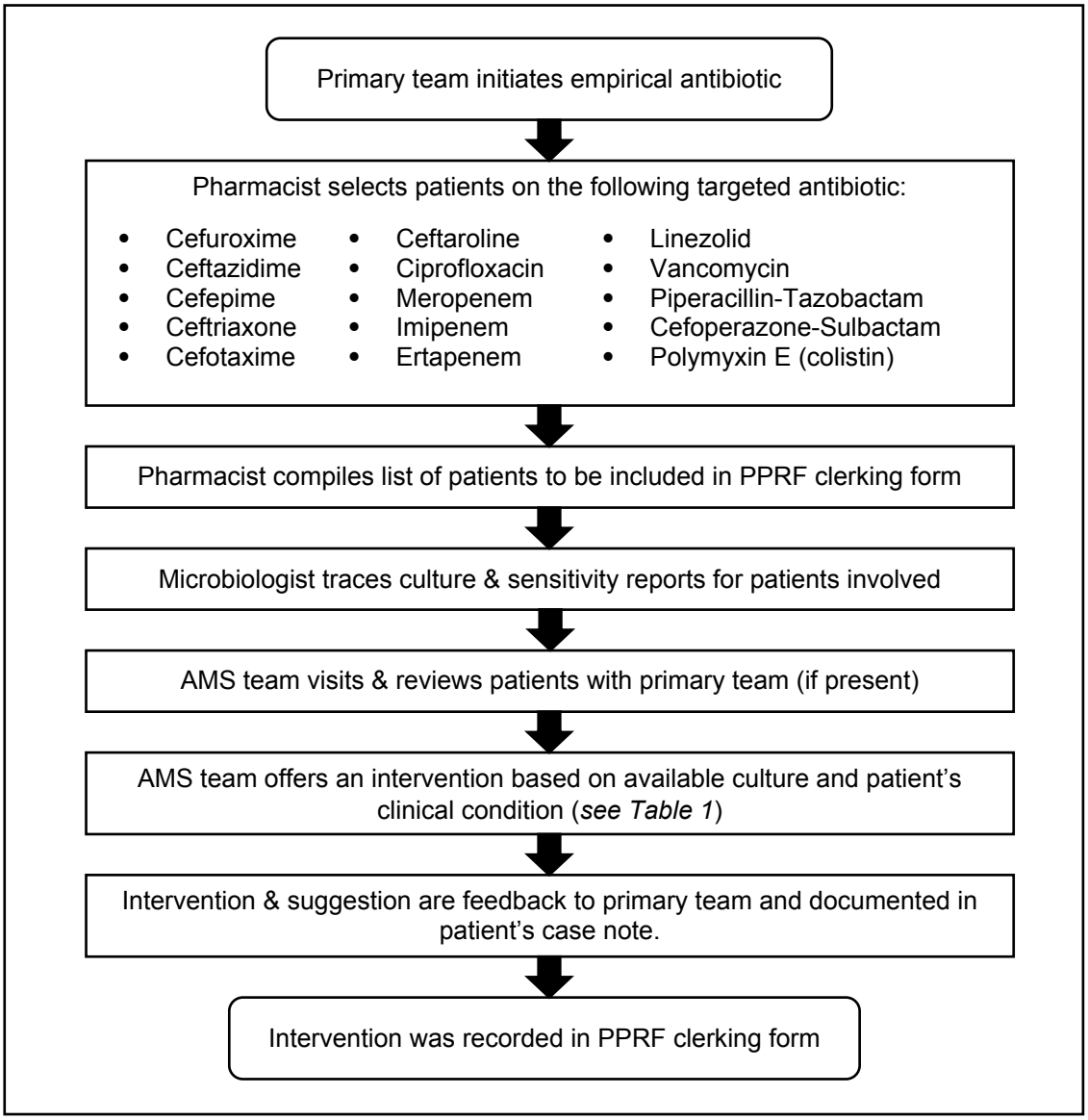

Figure 1: Post-prescription Review and Feedback (PPRF) workflow

During PPRF, the AMS team reviews the prescriptions, and provides feedback to guide the continuation, modification, or discontinuation of antibiotic therapy based on patient-specific factors and evolving clinical data. During the AMS rounds, the AMS team visits the identified patients, and reviews the prescriptions, microbiological culture results and patients' clinical condition. The AMS team may discuss among themselves to determine the appropriate interventions. Whenever possible, the discussions were conducted with the primary team responsible for the patients. . Feedback to guide the continuation, modification, or discontinuation of antibiotic therapy was communicated directly to the primary team and documented in the patients' case notes. The PPRF interventions were further defined in Table 1.

Table 1: Definition of interventions provided by the AMS team during PPRF

Intervention	Definition
Continue Empirically	To continue the current antibiotic regime as prescribed by the primary team while awaiting results for microbiological culture. The current antibiotic regime may change depending on the results of microbiological culture or clinical condition.
Continue Definitively	To continue the current antibiotic regime as prescribed by the primary team when it is definitively indicated. A planned duration may also be suggested by the AMS team.
De-escalate	The current antibiotic regime is changed from a broad-spectrum antibiotic to a narrower spectrum antibiotic or an antibiotic that induces less resistance.
IV to PO	An intravenous antibiotic is changed to an oral antibiotic of acceptable bioavailability.
Stop	The current antibiotic regime is stopped by the AMS team.
Escalate	The current antibiotic regime is changed to a broader spectrum antibiotic due to patient's deteriorating clinical condition or lack of response to current regimen.

Antibiotic Consumption

In this study, antibiotic consumption before and after the implementation of intensified PPRF intervention were compared. The total amount of intravenous antibiotics prescribed, measured in grams, was converted into defined daily doses (DDD) using the 2019 Anatomical Therapeutic Chemical Classification and Defined Daily Dose (ATC/DDD) index by the World Health Organization (WHO) (20). The DDD represents the assumed average daily maintenance dose of a drug when used for its main indication in adults. Antibiotic consumption, expressed as DDD per 1,000 patient days, during the pre-intervention period (July to December 2018) was compared to the post-intervention period (July to December 2019). 1,000The formula for DDD per 1,000 patient days was as below:

$$\frac{\text{Total antibiotic usage (grams) for adult per study period}}{\text{DDD (from WHO)}} = \text{Number of DDD per study period}$$

For 1,000 patient days:

$$\frac{\text{Number of DDD per study period}}{\text{Total number of patient days}} \times 1{,}000 = \text{Number of DDD per 1,000 patient days}$$

Statistical Analysis

The data was analysed using IBM SPSS Statistics version 22. Descriptive statistics were employed. Categorical variables were presented as numbers (n) and percentages (%), while continuous variables were expressed as means with standard deviations (SD) or medians with interquartile range (IQR), depending on the normality of the data. Independent t-test was used to compare the antibiotic consumption between the pre- and post-intervention periods. Statistical significance was set at $p < 0.05$.

Results

A total of 538 patients receiving the targeted antibiotics during the post-intervention period were included in the study, with 61% being men and a median age of 57 years (range: 41–68 years). During the 6-month post intervention period from July to December 2019, a total of 847 PPRF reviews were conducted. The average time from antibiotic initiation by the primary team to the AMS team review was 2.5 days (SD 2.3 days).

The characteristics of the reviews conducted during the PPRF process were summarised in Table 2. The majority of reviews were carried out in medical-based wards (46.3%) and surgical-based wards (26.8%). Respiratory tract infections were the most reviewed diagnosis (28.7%), followed by bone and joint infections (12.4%) and chemoprophylaxis (10.4%). The most frequently reviewed class of antibiotics were third-generation cephalosporins (32.2%), with ceftazidime (16.5%) and ceftriaxone (15%) being the most common. Ceftazidime was primarily indicated for tropical infections (5%, n=42 reviews), specifically for the empirical and definitive treatment of melioidosis, which is prevalent in Sabah. Ceftriaxone, on the other hand, was the preferred antibiotic for central nervous system infections (4.1%, n=35 reviews).

Table 2: Characteristics of PPRF reviews (n=847)

Characteristics	n (%)
Wards visited during PPRF	
Medical	393 (46.3)
Surgical	224 (26.8)
Intensive Care	115 (13.5)
Orthopaedic	112 (13.2)
Five most common diagnoses encountered	
Respiratory tract infection	243 (28.7)
Bone and joint infection	105 (12.4)
Chemoprophylaxis	88 (10.4)
Tropical infection	71 (8.4)
Central nervous system infection	48 (5.7)
Five most reviewed antibiotic groups prompting PPRF	
3rd generation cephalosporin	**273 (32.2)**
Ceftazidime	140 (16.5)
Ceftriaxone	127 (15.0)
Cefotaxime	5 (0.6)
Cefoprazone-Sulbactam	1 (0.1)
Penicillin/beta-lactamase combination	**228 (26.9)**
Piperacillin-Tazobactam	228 (26.9)
2nd generation cephalosporin	**123 (14.5)**
Cefuroxime	123 (14.5)
Carbapenems	**119 (14.0)**
Meropenem	116 (13.7)
Imipenenem	3 (0.4)
Ertapenem	0 (0.0)
4th generation cephalasoporin	**64 (7.5)**
Cefepime	64 (7.5)

The interventions made during the PPRF reviews are detailed in Figure 2. Among the 847 reviews, antibiotic de-escalation occurred in 264 cases (31.2%), antibiotics were continued definitively in 184 cases (21.7%), and therapy was stopped in 126 cases (14.9%). Respiratory tract infections accounted for the highest number of de-escalations, with 52 reviews (6.1%) leading to this intervention. Piperacillin-tazobactam was the most frequently de-escalated antibiotic, with 75 reviews (8.9%), followed by cefuroxime with 74 reviews (8.7%), and ceftriaxone with 51 reviews (6%).

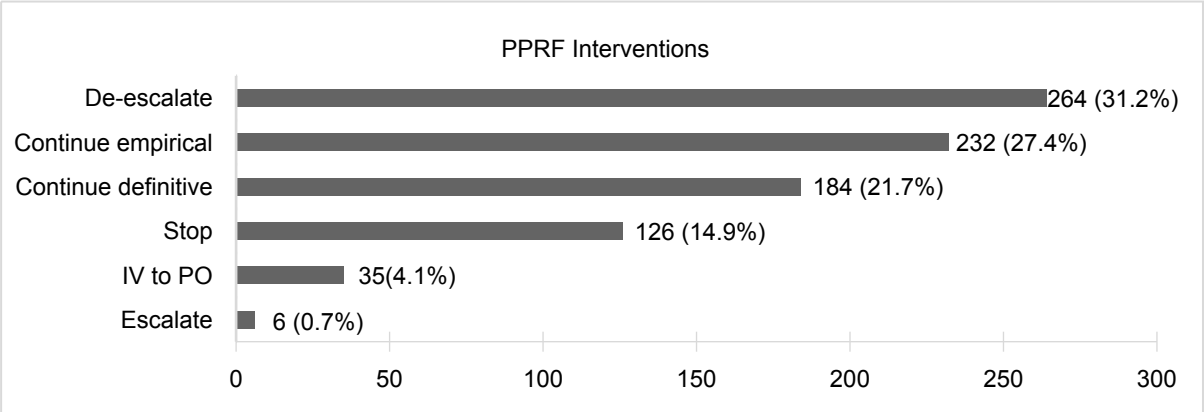

Figure 2: Interventions made by the AMS team during PPRF review

Antibiotics were continued either empirically or definitively in nearly half of the cases (49.1%). Among the third-generation cephalosporins, ceftazidime was the most frequently reviewed antibiotic, and it was also the most often continued (40 reviews, 4.7%) and stopped (39 reviews, 4.6%). Ceftazidime was

frequently continued empirically in respiratory infections (96 reviews, 11.3%) and definitively in tropical diseases, such as melioidosis (52 reviews, 6.1%).

Table 3 compares antibiotic utilisation before and after the implementation of the intensified PPRF intervention. The overall consumption of antibiotics, measured in DDD per 1,000 patient days, was significantly reduced by 56.3% (316.23 vs. 138.15 DDD per 1,000 patient days) during the post-intervention period from July to December 2019, compared to the pre-intervention period in July to December 2018 (p<0.001). Significant reductions were observed in the use of broad-spectrum antibiotics, including a 69.3% decrease in carbapenem consumption (p<0.001), a 44.8% reduction in piperacillin-tazobactam (p<0.001), and a 70.7% reduction in polymyxin E (p=0.009). Additionally, the utilisations of newly included cephalosporins in the intensified PPRF review, such as cefuroxime and ceftriaxone, were decreased by 77.4% (p=0.001) and 66.2% (p<0.001), respectively.

Table 3: Comparison of antibiotic utilisation during the pre- and post-implementation period of intensified PPRF, in DDD per 1,000 patient days

Antibiotic	Pre-PPRF [a]	Post-PPRF [a]	% change	p value [b]
2nd generation Cephalosporin				
Cefuroxime	88.57	20.06	-77.35	0.001
3rd generation Cephalosporin	118.84	66.47	-43.84	0.007
Ceftriaxone	77.26	26.12	-66.19	<0.001
Cefotaxime	0.74	0.92	24.32	0.65
Ceftazidime	40.59	39.27	-3.25	0.91
Cefoperazone-Sulbactam	0.26	0.11	-57.69	0.32
4th generation Cephalosporin				
Cefepime	14.16	9.31	-34.25	0.12
Carbapenems	31.67	9.72	-69.30	<0.001
Imipenem-Cilastin	1.27	0.15	-88.19	0.005
Meropenem	29.05	9.26	-68.12	<0.001
Ertapenem	1.37	0.31	-77.37	0.30
Anti-MRSA	7.75	3.97	-48.77	0.22
Vancomycin	6.6	3.62	-45.16	0.28
Linezolid	1.15	0.36	-68.70	0.18
Penicillin/Beta-lactam combination				
Piperacillin-Tazobactam	51.16	28.24	-44.80	<0.001
Others				
Polymyxin E (Colistin)	1.16	0.34	-70.69	0.009
Ciprofloxacin	2.89	0.08	-97.23	0.020
Total	316.23	138.15	-56.31	<0.001

[a] Pre-PPRF: July to December 2018; Post-PPRF: July to December 2019.
[b] Independent t-test
Abbreviation: DDD = Defined Daily Doses, PPRF = Post -Prescription Review and Feedback

Discussion

Our paper described the implementation of an intensified PPRF in a Malaysian specialist hospital and compare the antibiotic consumption before and after the intervention. PPRF has been shown to be an effective AMS strategy for reducing antibiotic consumption in many studies. In a 5-year descriptive study by Jover-Sáenz et al., conducted in a tertiary hospital, the implementation of an AMS program was associated with a 5.7% reduction in overall antibacterial consumption (21). Similarly, a systematic review by Kaki et al. reported that AMS interventions in critical care settings reduced antibiotic use by 11% to 38% in DDD per 1,000 patient-days (13). Our study demonstrated that by increasing the intensity of PPRF interventions, involving changing the once-weekly to twice-weekly reviews by a specialised AMS team, was associated

with a reduction in antibiotic consumption. This higher reduction may be attributable to the inclusion of antibiotic usage data from all general wards, not limited to intensive care units. Additionally, the high rate of antibiotic de-escalation recommended during PPRF rounds might have contributed to these findings.

A study conducted in Japan, using a similar PPRF intervention with a comparable AMS team composition but at a once-weekly frequency, also reported a reduction in antibiotic consumption (19). However, their PPRF focused solely on carbapenems and piperacillin-tazobactam, leading to an increased use of cefepime. In contrast, our study targeted a broader range of broad-spectrum antibiotics and involved twice-weekly reviews, resulting in reductions across various antibiotic classes, including carbapenems, piperacillin-tazobactam, cefepime, and polymyxin E (colistin). A high-intensity PAF strategy, like ours, was implemented in Canada with twice-weekly interdisciplinary rounds reviewing all internal medicine patients receiving any antimicrobial agent. This approach led to a 41.6% reduction in the overall antibiotic usage (22). These findings suggested that shifting from a lower-intensity strategy, which targets fewer antibiotics and is conducted less frequently, to a more frequent and comprehensive approach may result in a greater overall reduction in antibiotic consumption.

National data from 2008-2017 indicated that cephalosporins represented the highest-utilised class of antibiotics in Malaysia (5). Evidence suggested that cephalosporins contribute to the development of multidrug-resistant organisms, including extended-spectrum beta-lactamase (ESBL)-producing bacteria, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia (23)*. In our setting, cephalosporins comprised more than half of the antibiotics covered in the PPRF, with third-generation cephalosporins, specifically ceftazidime and ceftriaxone, being the most frequently reviewed antibiotics. We observed a notable reduction in the consumption of cefuroxime and ceftriaxone. A likely explanation for this reduction is the AMS team's active engagement with the primary team, who were mainly orthopaedic and general surgery departments, on the substitution of cefuroxime, which is commonly used for chemoprophylaxis with penicillin-based antibiotics or cefazolin. Similarly, ceftriaxone, often prescribed empirically for respiratory infections, was also switched to amoxicillin/clavulanate as the preferred option. This shift aligns with recommendations from the National Antimicrobial Guidelines 2019 (24) and is further reinforced by our local AMS policy. Supporting these findings, a study by Lester et al. in an urban hospital in Malawi demonstrated that an antimicrobial stewardship approach reduced third-generation cephalosporin prescriptions from 80.1% to 53.6% (25). Additionally, a Malaysian study showed that the appropriate use of third-generation cephalosporins increased significantly, from 77.1% to 95.8%, following AMS intervention (26). These findings highlighted the importance of targeted stewardship efforts in reducing the unnecessary use of cephalosporins, ultimately minimising antibiotic resistance pressure.

Choe and colleagues reported a 14.6% reduction in overall vancomycin use (37.6 DDD per 1,000 patient days vs. 32.1 DDD per 1,000 patient days) following intervention by the AMS team (27). In contrast, our study did not demonstrate a significant reduction in the use of anti-methicillin resistant staphylococcus aureus (MRSA) agents, particularly vancomycin. This outcome may be attributed to the relatively low prevalence of MRSA in Sabah, with an incidence rate of 0.12 per 100 admissions at HQE II, which is below the national target of less than 0.3 per 100 admissions (28). Consequently, empirical MRSA coverage is not routinely implemented. In our context, the initiation of anti-MRSA therapy is typically reserved for cases with positive cultures, and treatment is continued based on definitive microbiological evidence.

Similarly, we did not observe a significant decrease in ceftazidime usage between the pre- and post-intervention periods (40.59 DDD per 1,000 patient days vs. 39.27 DDD per 1,000 patient days). The primary indication for ceftazidime in our setting is for the empirical and definitive treatment of melioidosis, a condition with an incidence rate of 2.57 per 100,000 populations in Sabah (29) and an associated mortality rate of 25.6%. Given the high mortality rate, local health authorities advocate for the early initiation of ceftazidime in patients with known risk factors, such as diabetes mellitus, chronic lung disease (including old pulmonary tuberculosis), chronic renal failure, chronic alcoholism, thalassemia, patients who are on long term immunosuppressants (such as steroids or chemotherapy) and those with occupational exposure such as farmers, when they presented with pneumonia or sepsis symptoms (30). Additionally, when used for definitive treatment, the recommended high dose of 2g every six hours administered over an extended duration of 2 to 8 weeks contributed to the sustained elevated use of ceftazidime.

Our study acknowledged several limitations. Firstly, as a single-centre observational study, the findings cannot be generalisable to other settings with distinct patient populations, epidemiological profiles, and antibiotic prescribing practices. However, it is important to note that AMS interventions, as quality improvement initiatives, must be tailored to specific contexts. Our study provided some insights on the

potential efficacy of PPRF within the framework of our own setting. Secondly, the study was limited to a six-month duration. A longer follow-up period may yield more robust data regarding the sustainability of the PPRF programme and its long-term impact on antibiotic consumption. Furthermore, while interventions such as de-escalation were primarily guided by microbiological results, delays in obtaining these results might have impeded the timely treatment modifications, leading to prolonged antibiotic use. In our setting, it was not uncommon that certain cases of negative culture necessitated the outsourcing of the samples to another larger facility for further identification, with the results typically returning after a few weeks.

Although a reduced antibiotic consumption was observed after the implementation of intensified PPRF and AMS rounds, causality cannot be established. The study did not explore the potential confounding factors, including patient characteristics and concurrent AMS interventions that may have resulted in more restrictive antibiotic prescribing measures. This included formulary restrictions and pre-authorisation protocols, which may have also contributed to the observed reduction in antibiotic use. A controlled interrupted time-series analysis conducted in a vascular ward in Portugal found that a persuasive strategy, which was similar to our PPRF rounds, when implemented alongside existing restrictive interventions, contributed to a decrease in carbapenem consumption (31). Additionally, simultaneous infection prevention and control strategies aimed at preventing outbreaks of multi-drug-resistant organisms may have influenced the outcome data (32).

Moreover, the study's outcomes were limited to antibiotic consumption without assessing key patient-centred outcomes, such as clinical improvement or the economic impacts of the interventions. The study also did not investigate potential changes in antimicrobial resistance patterns over time. Nonetheless, previous research has demonstrated that reducing antibiotic consumption can improve clinical and economic outcomes, while also mitigating antimicrobial resistance (11, 33-34). Further research is warranted to evaluate the broader impact of PPRF, and the sustainability of implementing such a labour-intensive intervention. Future studies should also assess its long-term effects on mortality, infection rates, and antimicrobial resistance.

Conclusion

This study outlined the implementation of an intensified PPRF strategy within the hospital's AMS program. The combination of a more frequent review process and a dedicated AMS team could help to reduce antibiotic consumption, suggesting that a higher intensity approach may enhance AMS efforts. However, further research is needed to investigate the broader effects of PPRF, including its impact on patient clinical outcomes, local antimicrobial resistance patterns, and potential economic savings.

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Conflict of Interest

The authors declare that they have no conflicts of interest and they did not receive any financial support or funding that is relevant to this study.

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Prevalence and the Associated Factors of Proton Pump Inhibitor Co-Prescribed with Dual Antiplatelet Therapy among Adult Patients Diagnosed with Acute Coronary Syndrome upon Hospital Discharge

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Abstract

Introduction: There are conflicting evidence and expert opinion surrounding the co-prescription of proton pump inhibitor (PPI) and dual antiplatelet therapy (DAPT) among patients diagnosed with acute coronary syndrome (ACS).

Objective: This study aimed to determine the prevalence and factors associated with of PPI co-prescription with DAPT among patients diagnosed with ACS at hospital discharge.

Methods: A single-centre, cross-sectional study was conducted among adult ACS patients admitted to the general wards of Port Dickson Hospital between 1 January and 31 December 2021 who were discharged with DAPT (acetylsalicylic acid / glyprin and clopidogrel) with or without a PPI (pantoprazole). Simple and multiple logistic regression were used to determine the factors associated with PPI co-prescription with DAPT at discharge.

Results: Out of 322 included patients, the majority were male (68.3%), Malay (58.7%), and diagnosed with non-ST-elevation myocardial infarction (70.5%). A total of 234 (72.7%) patients were discharged with a co-prescription of PPI and DAPT. Patients who received PPI at admission were 26 times more likely to be co-prescribed with PPI and DAPT at discharge than those who did not (adjusted OR 26.00, 95% CI 11.52-58.70, p<0.001). Older patients and those with lower hemoglobin levels were more likely to receive a PPI co-prescription with DAPT (adjusted OR 1.04, 95% CI 1.01-1.06, p=0.006 and adjusted OR 0.82, 95% CI 0.72-0.95, p=0.007, respectively).

Conclusion: This study shown relatively high percentage of PPI prescription in ACS patients receiving DAPT. Further studies are warranted to determine the appropriateness of the PPI prescription.

Keywords: Proton pump inhibitor, dual antiplatelet therapy, acute coronary syndrome

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Introduction

The occurrence of acute coronary syndromes (ACS) involves a variety of life-threatening acute myocardial ischemic events caused by the rupture or erosion of an atherosclerotic plaque, as well as different levels of thrombosis and distal embolisation (1). The major cause of ACS is arterial thrombosis after the rupture or erosion of atherosclerotic plaque (2). ACS encompasses unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI) (3). The basis treatment for patients with acute coronary syndrome was dual antiplatelet therapy (DAPT) (4). Antiplatelet therapy was crucial for treating ACS because platelet adhesion, activation, and aggregation are key in forming arterial thrombi (5). The combined effects of two antiplatelet agents, that involve blocking COX-1 with aspirin and inhibiting the P2Y12 receptor, have been the focus of numerous clinical trials over the past decade. These trials have been conducted in patients diagnosed with ACS, including unstable angina, non-ST-elevation myocardial infarction, and ST-elevation myocardial infarction (2). Nevertheless, there was an unavoidable higher risk of bleeding as a side effect when dual antiplatelet medications are given. Bleeding from gastrointestinal peptic ulcers occurs 0.5% of the time, even among people using only low-dose aspirin

(6). Since DAPT increases the risk of gastrointestinal bleeding, many post-ACS patients were started on an H2 receptor antagonist or proton pump inhibitor (PPI).

PPIs are commonly used to lower the risk of gastrointestinal bleeding (7). PPI co-therapy has been shown to reduce the incidence of peptic ulcers and peptic ulcer complications in individuals receiving aspirin alone or in combination with clopidogrel, although it has the potential to affect the antiplatelet action of these drugs (8,9). The clinical use of PPIs along with clopidogrel is still under debates. In a statement released in November 2009, the U.S. Food and Drug Administration (FDA) advised against taking clopidogrel along with omeprazole and esomeprazole. The major reason for this was pharmacokinetic research which showed that concurrent omeprazole and clopidogrel may raise platelet reactivity levels in comparison to clopidogrel alone (10). When PPIs were used more widely and for longer periods, there was also greater concern about the potential negative effects such as developing clostridium difficile infections, osteoporosis and fractures (11). According to the 2016 American Heart Association targeted update, PPIs should only be given together with DAPT in patientswith a history of gastrointestinal bleeding (Class 1) and those at a higher risk of gastrointestinal bleeding, such as older patients, and those taking warfarin, steroids, or non-steroidal anti-inflammatory drugs (Class IIa). The regular use of PPIs was not recommended for patients at low risk of gastrointestinal bleeding (Class III: No Benefit) (12). In contrast, the European Society of Cardiology recommended using a PPI in conjunction with DAPT (13).

There has been a notable increase in the prescribing of PPIs among ACS patients who were receiving antiplatelet therapy. In our setting, observations made during daily practice suggested that a substantial number of patients may not have clinical indications to use PPIs. Furthermore, we notice an inconsistent pattern of PPI prescribing in ACS patients on DAPT at the time of hospital discharge. There was a lack of local published data regarding the prevalence of PPI co-prescription with DAPT, and the predictors of PPI prescribing among ACS patients receiving DAPT (14). Therefore, this study aimed to determine the prevalence and explore the factors associated with PPI co-prescription with DAPT among patients diagnosed with ACS at hospital discharge. Our findings may be able to help in establishing local guidelines to improve prescribing practices and ensure rational drug use.

Method

Study design and study subjects

This study was a single-centre, cross-sectional study conducted among adult ACS patients admitted to the general wards of Port Dickson Hospital in Negeri Sembilan, Malaysia who were discharged with DAPT (acetylsalicylic acid / glyprin and clopidogrel) with or without a PPI (pantoprazole). The list of patients hospitalised for ACS between 1 January and 31 December 2021 was obtained from the hospital admission record and arranged chronologically in Microsoft Excel. Only the first admission episode of patients with multiple hospital admissions were selected. Subsequently, computer-generated random numbers were used to enroll potential study subjects. Subjects were eligible for inclusion in the study if they were adults (aged 18 years or older) diagnosed with ACS and had received DAPT. Patients who did not complete ACS treatment due to a change of diagnosis, concurrent use of anticoagulation, and non-Malaysians were excluded from the study.

The sample size of study subjects required was calculated based on a 5% margin of error, 95% confidence interval, 32% response distribution (based on a previous study in Qatar) (14), and 1,400 inpatient general ward admissions in 2021. A total of 269 study subjects were needed. This study was registered with the National Medical Research Registry, Ministry of Health Malaysia (NMRR 21-02303-JIJ) and approved by the Medical Research Ethics Committee, Ministry of Health Malaysia before the commencement of this study.

Data collection

A standardised data collection form was used. It consisted of four parts: (A) socio-demographic and clinical information, including age, gender, race, smoking status, alcohol intake, and hemoglobin level at admission; (B) past medical history, including diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease; (C) types of ACS (STEMI, NSTEMI and UA); (D) prescription of PPI at admission and the list of discharge medications. All required information were extracted from the Pharmacy Information System (PhIS) prescription database and Hospital Information System (HIS).

Data analysis

Data collected were tabulated in the International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) version 26 for further analysis. Normality test was performed for continuous variable (age and hemoglobin). Descriptive and inferential statistics were employed for the data analyses. Continuous data were presented as mean and standard deviation (SD), while categorical data were presented as numbers (n) and percentages (%). Simple logistic regression analysis was performed on all variables. Variables with *p*-value less than 0.25 in the simple logistic regression were subsequently included in a multiple logistic regression model to determine significant factors associated with PPI co-prescription with DAPT at discharge. The adjusted odds ratios (OR) with 95% confidence interval (CI) were presented, with a *p*-value of <0.05 considered statistically significant.

Results

A total of 404 subjects met the inclusion criteria. However, 82 subjects were not included in the study due to insufficient data. Therefore, only 322 patients were included. Table 1 presented the characteristics of included patients. The majority of the subjects were Malay, male, admitted for NSTEMI, and already on PPI use at admission. The mean age and hemoglobin level at admission were 57.35 years old and 12.8g/dL respectively. Common comorbidities were diabetes mellitus, hypertension, and chronic kidney disease. The prevalence of PPI co-prescription with DAPT at discharge was 72.7%. Elderly (65 years or older) comprised 35.4% of PPI users. (Table 2).

Table 1: Baseline and treatment-related characteristics of study subjects (N=322)

Variables	n (%)	Mean (SD)
Age, year		57.35 (13.64)
≥ 65 years	98 (30.4)	
< 65 years	224 (69.6)	
Race		
Malay	189 (58.7)	
Chinese	39 (12.1)	
Indian	91 (28.3)	
Others	3 (0.9)	
Gender		
Male	220 (68.3)	
Female	102 (31.7)	
ACS		
STEMI	24 (7.5)	
NSTEMI	227 (70.5)	
UA	71 (22)	
Smoking status		
Yes	65 (20.2)	
No	200 (62.1)	
Unknown	57 (17.7)	
Alcohol status		
Yes	11 (3.4)	
No	239 (74.2)	
Unknown	72 (22.4)	
Diabetes Mellitus		
Yes	201 (62.42)	
No	121 (37.58)	
Dyslipidemia		
Yes	43 (13.4)	
No	279 (86.6)	
Hypertension		
Yes	224 (69.6)	
No	98 (30.4)	
Chronic kidney disease		
Yes	74 (22.9)	
No	248 (77)	

Hb at admission, g/dL		12.8 (2.54)
PPI at admission		
Yes	176 (54.7)	
No	146 (45.3)	

Abbreviations: SD = standard deviation; ACS = acute coronary syndrome; STEMI = ST-elevation myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; UA = unstable angina; Hb = haemoglobin; PPI = proton pump inhibitor.

Table 2: PPI prescription at hospital discharge (N=322)

Characteristics	Received PPI (n=234), n (%)	No PPI (n=88), n (%)
Gender, n (%)		
Male	158 (71.8)	62 (28.2)
Female	76 (74.5)	26 (25.5)
Age, year ,mean (SD)	59.34 (13.23)	52.06 (13.38)
≥ 65 years	83 (84.7)	15 (15.3)
< 65 years	151 (67.4)	73 (32.6)
Race, n (%)		
Malay	136 (72.0)	53 (28.0)
Non–Malay	98 (73.7)	35 (26.3)
Smoking status, n (%)		
Yes	48 (73.8)	17 (26.2)
No / Unknown	186 (72.4)	71 (27.6)
Alcohol status, n (%)		
Yes	8 (80.0)	2 (20.0)
No / Unknown	226 (72.4)	86 (27.6)
Diabetes Mellitus, n (%)		
Yes	148 (73.6)	53 (26.4)
No	86 (71.1)	35 (28.9)
Dyslipidemia, n (%)		
Yes	30 (69.8)	13 (30.2)
No	204 (73.1)	75 (26.9)
Hypertension, n (%)		
Yes	163 (72.8)	61 (27.2)
No	71 (72.4)	27 (27.6)
Chronic kidney disease, n (%)		
Yes	61 (82.4)	13 (17.6)
No	173 (69.8)	75 (30.2)
ACS type, n (%)		
STEMI	20 (83.3)	4 (16.7)
NSTEMI / UA	214 (71.8)	84 (28.2)
Hb at admission, g/dL, mean (SD)	12.43 (2.60)	13.78 (2.10)
PPI at admission, n (%)		
Yes	168 (95.5)	8 (4.5)
No	66 (45.2)	80 (54.8)

Abbreviations: SD = standard deviation; ACS = acute coronary syndrome; STEMI = ST-elevation myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; UA = unstable angina; Hb = haemoglobin; PPI = proton pump inhibitor.

The logistic regression analysis was presented in Table 3. Simple logistic regression showed statistically significant associations between age (p<0.001), hemoglobin level at admission (p<0.001), presence of chronic kidney disease (p=0.034), and use of PPI at admission (p<0.001) with PPI co-prescription with DAPT at hospital discharge. The multiple logistic regression model showed a statistically significant association between age, hemoglobin level at admission, and the use of PPI at admission with PPIs co-prescription with DAPT at hospital discharge. No interactions and multicollinearity were found among the independent variables in this study. Patients who received PPI at admission were twenty-six times more likely to be co-prescribed with PPI and DAPT at discharge than those who did not receive PPI on admission (adjusted OR 26.00, 95% CI 11.52-58.70, p<0.001). Older patients and patients with lower hemoglobin

levels were more likely to get PPI co-prescription with DAPT at discharge (adjusted OR 1.04, 95% CI 1.01-1.06, p=0.006 and adjusted OR 0.82, 95% CI 0.72-0.95, p=0.007, respectively).

Table 3: Factors associated with the co-prescription of PPI and DAPT at discharge

Variables	Simple Logistic Regression			Multiple Logistic Regression		
	(b)	Crude OR (95% CIs)	p-value	(b)	Adjusted OR (95% CI)	p-value[d]
Gender						
Male	0	1.00				
Female	0.14	1.15 (0.67-1.96)	0.614			
Age, year (mean)	0.04	1.04 (1.02-1.06)	**<0.001**	0.04	1.04 (1.01 – 1.06)	**0.006**
Race						
Malay	0	1.00				
Non–Malay	0.09	1.09 (0.66– 1.80)	0.732			
Smoking status						
Yes	0	1.00				
No/Unknown	-0.08	0.93 (0.50–1.72)	0.812			
Alcohol Status						
Yes	0	1.00				
No/Unknown	-0.42	0.66 (0.14–3.16)	0.600			
Diabetes Mellitus						
Yes	0	1.00				
No	-0.13	0.88 (0.53– 1.46)	0.618			
Dyslipidemia						
Yes	0	1.00				
No	0.16	1.18 (0.58- 2.38)	0.647			
Hypertension						
Yes	0	1.00				
No	-0.02	0.98 (0.58–1.68)	0.953			
Chronic Kidney Disease						
Yes	0	1.00		0	1.00	
No	-0.71	0.49 (0.26–0.95)	**0.034**	-0.36	0.70 (0.30-1.60)	0.397
ACS type						
STEMI	0	1.00		0	1.00	
NSTEMI/UA	-0.67	0.51 (0.17-1.54)	**0.231**	-0.32	0.73 (0.18-2.93)	0.656
Hb at admission, g/dL (mean)	-0.23	0.80 (0.72-0.89)	**<0.001**	-0.19	0.82 (0.72-0.95)	**0.007**
PPI on admission						
No	0	1.00		0	1.00	
Yes	3.24	25.46 (11.66–55.56)	**<0.001**	3.26	26.00 (11.52-58.70)	**<0.001**

[d] Backward Multiple Logistic Regression model was applied

Constant 0.393

Multicollinearity and interaction term were checked and not found

Hosmer and Lemeshow Test, p=0.216; Classification table 82.0%; Area under ROC curve 0.883

Abbreviations: OR = odds ratio; CI = confidence interval; ACS = acute coronary syndrome; STEMI = ST-elevation myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; UA = unstable angina; Hb = haemoglobin; PPI = proton pump inhibitor.

Discussion

This study was carried out to assess the prevalence and associated factors of PPI co-prescription with DAPT at the time of hospital discharge among patients diagnosed with ACS. In this single-centre study, the percentage PPI and DAPT co-prescription at discharge was 72.2%. According to Ho et al. (2009), the prevalence of PPI co-prescriptions with clopidogrel among ACS patients at discharge in 127 Veteran Affair Hospital was 63.7%. The study reported that compared to clopidogrel use alone, concurrent use of PPI and clopidogrel for ACS was linked to a greater risk of unfavorable outcomes (9). Different findings were reported by a study in Qatar in 2016 whereby only 32% of the patients who were on DAPT were discharged with PPI (14). Other studies reported that 31 to 33% of ACS patients were co-prescribed with DAPT and PPIs (15, 16).

In our study, ACS patients who were older, had chronic kidney disease, lower hemoglobin levels, and on PPI at admission were significantly associated with PPI use in addition to DAPT at discharge. According to a previous study by Queen et al. in 2018, the severity, fatality, and functional outcome of bleeding in patients on long-term antiplatelet therapy worsen as patients age. The study results indicated that over 80% of elderly patients above 65 years old were prescribed with PPI upon discharge, suggesting the commonality of PPI prescriptions among the elderly (17). Deshpande, Admane, and Mardikar (2018) from the Spandan Heart Institute and Research Center mentioned that recognided factors contributing to an increased risk of bleeding include advanced age (over 75 years), history of prior bleeding, and a previous stroke (18). Nonetheless, because elderly people were more likely to be unwell and need to be hospitalised, age was not generally regarded as an independent determinant in PPI prescription. Research indicated that the elderly may be overprescribed PPIs, which could result in osteoporosis and fractures if the medication was taken for longer than eight weeks. Elderly patients were also at a higher risk of contracting Clostridium *difficile* infections (CDI) (19). The 2015 AGS Bears Criteria have included PPI as a potentially inappropriate medication for older adults, as a measure taken by the American Geriatrics Society (AGS) to reduce unnecessary prescribing of PPIs in this population (19).

The second factor associated with the co-prescription of DAPT and PPI was chronic kidney disease. The presence of chronic kidney disease was statistically significant in simple logistic regression, but not in multiple logistic regression. Exposure to PPIs was linked to an increased risk of acute kidney injury, chronic kidney disease progression, and end-stage renal disease (ESRD). Due to the high prevalence of PPI use and long-term negative consequences, PPI deprescribing must be prioritised to lessen the harm and burden (20). PPI use has also been linked to an increased incidence of chronic kidney disease according to Xie et al. (21). However, given that most of the patients in this study were white men, the results of this study might not be generally applicable. According to a survey by Carrero et al., a greater percentage of patients received noninvasive treatment as renal function deteriorated. The study found that proton pump inhibitors and calcium channel blockers were more frequently used in patients with worsening kidney function (22). When age, diabetes, hypertension, hyperlipidemia, angiotensin-converting enzyme (ACE) inhibitor, diuretic, and H2-receptor blocker use were taken into account, PPI use was linked to a 1.2-fold increased risk of chronic kidney disease compared to non-users. The study also found that patients who were exposed to PPIs had a noticeably greater incidence rate of chronic kidney disease than patients who did not take PPIs (20).

The third factor associated with the co-prescription of DAPT and PPI was low hemoglobin at admission. The results of our study were in line with another Asian study, where the primary cause of inappropriate PPI prescription was anemia (23). Fah et al. stated in their study that stress ulcer prophylaxis was the most common indication, while anemia with no evidence of gastrointestinal bleeding was the main non-indication for starting PPIs (12). Several clinical studies suggested that starting PPIs regularly for anemia patients was not advisable because this could cause hyposecretion of gastric acid and impair the absorption of iron (24). Meanwhile, the low reading of hemoglobin did not necessarily indicate gastrointestinal blood loss (18). Still, studies indicated that anemia may play a significant role in inappropriate PPI prescribing (25).

The final factor associated with the co-prescription of DAPT and PPI was PPI prescribed at admission. Patients who were already on PPI during admission were more likely to be discharged with PPI. In a study conducted in Qatar by Awaitsu et al. (2016), it was found that patients who were prescribed with PPIs upon admission were at least 16 times more likely to be prescribed PPIs at discharge compared to those who did not receive PPIs at admission (14). In our study, patients who received PPI at admission were 28 times more likely to be co-prescribed with DAPT than those patients who did not receive PPI at

admission. According to a study by Gamelas et al. (2019), almost half of the patients (46.5% at admission and 55% at discharge) were receiving PPI, even though more than half of them did not need it. The primary cause of the overprescription of PPI was ulcer prevention in individuals at low risk (25). These findings were consistent with another study which stated that gastrointestinal bleeding prophylaxis was the most common inappropriate indication, even though the medical records did not specify clinical evidence for such indication (26).

There were several limitations for this study. Firstly, it was a single-centre study, limiting the generalisability of the study results. Secondly, there was a chance that significant historical and clinical data were overlooked when collecting retrospective data from the patient medical records. Several crucial pieces of information or factors related to the use of PPIs should be considered, including a history of prior gastrointestinal bleeding and concurrent use of over-the-counter non-steroidal anti-inflammatory drugs (NSAIDs), a history of pelvic ulcer disease, Helicobacter pylori infection, gastroesophageal reflux disease (GERD), and the use of PPIs at the time of admission, may have been completely missing from the medical records. Thirdly, we did not capture the patient outcomes of taking concurrent PPI and DAPT. Lastly, the results could have been influenced by additional unidentified confounders. Despite these drawbacks, the study has added valuable information about the prevalence of PPI use in the Malaysian setting and can be used as a reference for future research. A future study may be conducted to explore the reason behind the prescribing of PPI among patients treated for ACS in Malaysia and assess the long term outcomes of taking PPI together with DAPT.

Conclusion

The study's findings demonstrated that PPI use was prevalent among ACSpatients receiving DAPT in this district hospital. The associated factors of co-prescribing PPI with DAPT at hospital discharge were older age, lower hemoglobin levels, and the use of PPI at admission. However, given the constraints in the study design, these predictors were not definitive. More research is needed to identify the cardiovascular outcomes of this treatment combination and look into the appropriateness of PPI co-prescription with DAPT in ACS patients.

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Conflict of interest

No funding was received for this study. The authors have no conflict of interest to disclose.

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Assessment of Patients' Willingness to Pay for Drugs for Non-Communicable Diseases in Senawang Health Clinic

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Abstract

Introduction: The cost for healthcare is on the rise in most countries including Malaysia. With the increased burden of diseases, drug expenditure increases simultaneously. As medicines in the Ministry of Health Malaysia facilities are highly subsidised by the government, alternative medicines financing mechanism to help cover these costs may be required in the coming future.
Objective: To assess patients' willingness to pay (WTP) for drugs for non-communicable diseases (NCD) in Senawang Health Clinic, Negeri Sembilan and determine its' influencing factors.
Methods: This was a cross-sectional study conducted from April to June 2022. A self-administered questionnaire was used to assess patients' WTP for NCD drugs and the factors. The associations between patient's sociodemographic characteristics and factors affecting their WTP were analysed.
Results: A total of 390 patients participated in this survey. Most patients (70.5%) disagreed if government implements drug payment charges. The number of dependents and the disease severity were significantly associated with the WTP for NCD drugs. The number of dependents and the income level demonstrated a significant association with WTP for drugs if additional services were offered at KK Senawang. Income, gender, education level and disease severity were not associated with the WTP.
Conclusion: Assessing factors that influence the WTP may help the government to propose an effective and sustainable medicine financing mechanism.
Keywords: Willingness to pay, non-communicable diseases, factors

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Introduction

The rise of non-communicable diseases (NCDs) was stemming from the changes in lifestyle and diet, as well as ageing of the population. The prevalence of NCDs generally increases with age and causes an increase in the demand for healthcare services which are associated with higher healthcare costs. NCDs are also known as chronic diseases which are generated from a combination of genetic, physiological, environmental and behavioral factors that cause people to suffer for a long period (1). NCDs killed 41 million people each year, which accounted for 71% of all deaths globally. Cardiovascular diseases accounted for most NCD deaths, or 17.9 million people annually, followed by cancers (9.3 million), respiratory diseases (4.1 million), and diabetes (1.5 million) (1). Two thirds of the Malaysian population have a least one of three NCDs, namely diabetes, hypertension or hypercholesterolemia (2). More than a quarter have at least two NCDs and almost 10 percent have all three. Willingness to pay (WTP) was defined as the amount of money a person is willing to spend for medical interventions in order to have a better health outcome of his or her disease conditions (3). It was a concept being used increasingly to inform policy decisions in the health sector. WTP can also estimate the fair price of medical services from the consumers' point of view and determine the population's acceptance and their agreement to contribute financially to access healthcare services.

Malaysia has a dichotomous healthcare system that consists of a highly subsidised public sector and a private sector that is funded mainly by patients' own out-of-pocket payment and private health insurance. With more than half of the populations seeking care from the government clinics and hospitals, the public sector facilities are constantly facing financial pressure (4). The financial constraints become

more prevalent with the constant surge of medicines prices and medicine expenditure, that is resulted by multiple factors, such as aging population, higher consumer expectations, long-term drug treatment for chronic conditions, polypharmacy, improvements in diagnostics or treatment of diseases, and novel expensive drugs offered due to advancement of health technology (5).

Medications provided in the Ministry of Health (MOH) facilities receive full government subsidies, irrespective of patients' income level and their ability to pay. This medicine financing mechanism may not be sustainable in the long term. While it is essential to preserve health services as equitable and affordable for all, including the poor, sustainability must be ensured. Many countries have already introduced co-payment systems for cost recovery. Nevertheless, any proposals for medicines cost sharing must be carefully considered. For example, investigating the WTP for medicines can help decision makers to understand the preferences for pharmacy services among our local population. There may be certain factors that affect patient's WTP such as age, gender, education status, number of dependents and more (6). Therefore, this study was carried out to assess patients' WTP for NCD drugs and to determine the factors influencing patients' WTP. This study may serve as preliminary evidence in proposing a co-payment or any cost sharing mechanisms in the MOH.

Method

This was a cross-sectional study to assess patients' WTP for NCD drugs in Senawang Health Clinic (KK Senawang), Negeri Sembilan. This study was conducted from 1st April to 1st June 2022. The study was registered under the National Medical Research Registry (NMRR ID-22-00101-TDQ) and the ethical approval was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (MOH).

In this study, a structured questionnaire was adapted from a local study (4). Permission was obtained from the author to use the questionnaire in this study. The study instrument was readily available in both English and Malay language. Questions that were beyond the scope of our study were removed from the original questionnaire. A pilot study was carried out to validate the modified questionnaire, which was disseminated among 30 respondents consisting of family medicine specialist (FMS), doctors and pharmacists from KK Senawang for content validation. This aimed to analyse the clarity of the questions, wordings and titles. Cronbach's Alpha was applied to determine the reliability and internal consistency of the modified questionnaire. The obtained Cronbach's Alpha value was 0.705 which indicated a high level of internal consistency.

The final questionnaire comprised two sections. Part 1 collected socio-demographics information of the respondents, whereas Part 2 consisted of five questions regarding patients' willingness to pay for drug charges with response recorded as either "yes" or "no", and questions about patients' willingness to pay for drugs if additional services were provided with multiple-choice answers.

The questionnaire was disseminated to the patients with NCDs who attended KK Senawang during the study period. Random sampling was applied in this study, using a lottery method to select patients. In this method, the researcher drew numbers from the box containing slips of paper numbered one to ten. The randomly chosen number determined the n-th patient to be approached at the screening counter of Outpatient Pharmacy at KK Senawang. After screening for inclusion and exclusion criteria, a brief explanation of the study's objectives was provided to every potential respondent, and they were required to complete the consent form before participating. They were also given the option to choose their preferred language for the questionnaire. Patients answered the questionnaire while waiting for their medications to be prepared, and returned the completed questionnaire to the dispensing pharmacists.

The Raosoft Software was used to attain the recommended sample size for this study. With a 5% margin of errors and 95% confidence interval, population size was set to 20,000 and response distribution of 50%. The recommended sample size calculated was 383. The included study population were patients with diabetes mellitus, hypertension and/or hyperlipidaemia, from age group from 25 to 60 years old with the ability to read and understand Bahasa Melayu or English. Patients from age group of 25-60 was chosen to represent average starting age of employment up until retirement age. In contrast, patients from the Maternal and Child Health Clinic with NCDs, patients with psychiatric illnesses, healthcare staffs, and foreigners were excluded from the study.

IBM SPSS Statistics version 26 was used to analyse the data. Normality was assessed and the associations between the study variables were tested for statistical significance using chi square (X^2) test. Data collected from the sociodemographic section was described using descriptive statistics. Association

was also tested between sociodemographic data and WTP for medications if additional services were provided in healthcare. A p-value <0.05 was considered statistically significant.

Results

A total of 400 patients were approached. Excluding incomplete questionnaires, a total of 390 patients participated this study with a response rate of 97.50%. Majority of the patients (33.3%) were aged 50-54. More than half of the patients were female. Most patients (36.1 %) had diploma education level, followed by degree (25.6 %) and secondary school (14.4%) (Table 1). The total amount of money spent for medication and treatment per month ranged from RM0 to RM500 with a mean of RM144.50.

Table 1: Patient's demographical characteristics (n=390)

Socio-demographic	n (%)
Age (years)	
25-29	12 (3.1)
30-34	10 (2.6)
35-39	13 (3.3)
40-45	49 (12.6)
46-49	99 (25.4)
50-54	130 (33.3)
54-59	77 (19.7)
Gender	
Male	186 (47.7)
Female	204 (52.3)
Ethnicity	
Malay	205 (52.6)
Indian	69 (17.7)
Chinese	104 (26.7)
Others	12 (3.1)
Marital status	
Married	259 (66.4)
Single	100 (25.6)
Widow/widower	31 (7.9)
Education level	
Primary School	52 (13.4)
Secondary School	56 (14.4)
Diploma	141 (36.1)
Degree	100 (25.6)
Master	41 (10.5)
PHD	0
Number of dependents	
Less than 3	151 (38.7)
Three and above	239 (61.3)
Household Income	
< RM5,000	252 (64.6)
RM5,000 – 10,000	85 (21.6)
> RM10,000	53 (13.6)
Diseases	
Diabetes Mellitus	240 (61.5)
Hypertension	273 (70.0)
Hyperlipidemia	232 (59.5)

Majority of patients (70.5%) disagreed on implementing drug charges and most of them (64.6%) preferred the charges to be in accordance with one's salary. Most of the patients (58.5%) said that severity of the disease affects their ability to pay for drugs (Table 2). Besides that, nearly half of the patients (53.3%) expressed a preference for a system where services are received based on ability to pay. However, the majority disagreed with the concept of paying half of the actual price for drugs consumed (76.7%) (Table 3).

Table 2: Patients' WTP for NCD drugs

Questions	n (%)
Agree on implementation of drug charges	
Yes	105 (26.9)
No	275 (70.5)
Unsure	10 (2.6)
Drug payment charges depending on salary	
Yes	252 (64.6)
No	119 (30.5)
Unsure	19 (4.9)
Severity of disease affects WTP	
Yes	228 (58.5)
No	125 (32.0)
Unsure	37 (9.7)
Expenditures affected due to drug payment	
Yes	327 (82.8)
No	63 (17.2)

Table 3: Patients' suggestions for improving MOH's medicine financing system

Questions	n (%)
Increase government fee from RM1-RM5	
Yes	178 (45.7)
No	212 (54.3)
Pay half of the actual price for drugs	
Yes	91 (23.3)
No	299 (76.7)
High charges for registration depending on salary	
Yes	112 (28.7)
No	278 (71.3)
Health services based on ability to pay	
Yes	208 (53.3)
No	182 (46.7)

Referring to Table 4, patients were then asked about their willingness to contribute to drug payment charges if additional services were offered at KK Senawang. The majority of patients expressed interest in receiving express number at pharmacy counter (57.5%) followed by drive-thru option (56.2%), medications delivered by post (46.4%) and for being involved in decision making (37.7%).

Table 4: WTP for drugs if additional services were offered in KK Senawang

Additional services	n (%)
Drive Thru	
Yes	219 (56.2)
No	171 (43.8)
Involved in decision making process with doctor	
Yes	147 (37.7)
No	243 (62.3)
Receive medication through postage	
Yes	181 (46.4)
No	209 (53.6)
To choose brand of medication	
Yes	93 (23.8)
No	297 (76.2)
Express number at pharmacy	
Yes	224 (57.5)
No	166 (42.6)

There was a significant association between the severity of disease and number of dependents with WTP for drugs (p-value 0.03 and 0.01, respectively). However, there was no association between gender, income and education level with WTP for medication, as shown in Table 5. In addition, the relationship between sociodemographic data and WTP for medications when additional services were provided in healthcare settings was analysed. The data indicated that the number of dependents and level of income significantly affected WTP for medications if additional services were provided, whereas gender, education level and severity of diseases did not have any significant association (Table 6).

Table 5: Association between sociodemographic factors and WTP for drugs

Sociodemographic factors	Yes	No	Unsure	Total	*p*-value [a]
Gender					
Male	52	131	3	186	0.498
Female	53	144	7	204	
Education level					
Primary school	16	40	0	56	0.522
Secondary school	71	164	6	241	
Diploma	16	54	3	73	
Degree	2	16	1	19	
Masters	0	1	0	1	
Dependents					
Below three	39	60	3	102	**0.010**
Three	33	115	1	149	
Above three	33	100	6	139	
Income					
>RM10,000	11	42	0	53	0.120
RM5,000 – 10,000	26	59	0	85	
<RM5,000	68	174	10	252	
Severity of disease					
Yes	68	156	4	228	**0.030**
No	35	87	3	125	
Unsure	2	32	3	37	

[a] Chi-square (X^2) analysis

Table 6: Association between sociodemographic factors and WTP for drugs if additional services were offered in KK Senawang

Sociodemographic factors	Yes	No	Total	*p*-value [a]
Gender				
Male	112	74	186	0.442
Female	115	89	204	
Education level				
Primary school	29	27	56	0.136
Secondary school	139	102	241	
Diploma	42	31	73	
Degree	16	3	19	
Masters	1	0	1	
Dependents				
Below three	71	31	102	**0.020**
Three	71	78	149	
Above three	85	54	139	
Income				
>RM10,000	24	29	53	**0.039**
RM5,000 – 10,000	47	38	85	
<RM5,000	156	96	252	
Severity of disease				
Yes	134	94	228	0.639
No	69	56	125	
Unsure	24	13	36	

[a] Chi-square (X^2) analysis

Discussion

This study was conducted to assess patients' WTP for NCD medications and to determine the factors influencing their WTP. A high proportion of respondents expressed disagreement on the implementation of medication charges. This is not a surprising findings as the patients are currently enjoying free medications from the MOH health facilities, regardless of their ability to pay. The severity of disease had a significance association with the WTP for NCDs' drugs. This showed that patients who prioritise their health were more willing to pay extra money to improve their condition. For diseases with high risks of morbidity, mortality and increased costs of future care, educating patients about the benefits of specific treatments may enhance their perceived value of these therapies and increase patient WTP. In a study on COPD patients, those with severe or very severe COPD were willing to pay more for symptom relief (5). This may be due to a heightened awareness of their symptoms and their impact among those with more severe disease. Similarly, a study conducted by Kawata et al. found that patients were willing to pay more per month to reduce the number of hypoglycaemic events from three per month to none (6).

Income showed a significant association with WTP for drugs if additional services were offered in KK Senawang. This may be because people with steady income sources are more capable of making regular payments than those with uncertain or irregular income. Using Malaysia's average household gross monthly income (RM7,901.00) and middle income (RM5,873.00) in 2019 published by the Department of Statistics Malaysia as a reference, more than half of our respondents' (57.0%) household monthly income were at the lower end of the income distribution. Higher-income individuals were generally more able to spend, resulting in a high WTP. A study conducted in 2018 showed that those were employed presented higher WTP for healthcare services compared to those who were unemployed (7). Similarly, a study by Aziruddin in 2018 found that patients with higher incomes were more willing to pay for healthcare services leading to an increased service utilisation (8). This indicated that economic resources serve as a determinant for WTP that is independent of the morbidity and mortality risk associated with a given disease (10). Therefore, it is important to consider the economic factor when establishing pricing models, especially for diseases with higher long-term health risks that could ultimately results in higher patient care costs over time (11).

From our analysis, education level was not associated with the WTP for medications with or without additional services. However, other studies have shown a link between the higher education level and increased WTP due to greater awareness of the benefits of treatments. For instance, patients with better education were willing to pay for post-operative antiemetic therapy due to their understanding of its advantages (12). Also, patients with professional degrees, or with one or more comorbid conditions were more likely to pay for a disease-modifying therapies. Furthermore, another study concluded that education level and WTP for psoriasis treatment was significantly associated towards each other as patients with higher education levels may be engaged in work-related activities in which their physical appearance may impact their ability to succeed or achieve career advancement. Someone with higher education tend to process information more effectively which could influence their knowledge in a matter, including in the utilisation of health services (13).

Our study found that there was a significant association between the number of dependents in a household and the WTP for drugs, including when additional services were provided. Those with a high number of dependents would have more responsibilities and higher household expenses, which may lead to hesitancy in paying for medications. A study on WTP for lung cancer treatment stated that patients with family around to take care of, were significantly more willing to pay as compared with those without dependents (14). It was also noted that those with high number of dependents were more willing to pay for luxuries such as vacation and shopping rather than for healthcare. By providing services such as Drive-thru, medication postage, or express pharmacy counter, may reduce the need for patients to visit pharmacy in person, saving their time and effort. These may encouraged them to be more willing to pay for this services, which would also reduce the burden of prescription handling and waiting times.

There were several limitations in this study. The results in this study were only limited to patients in a single health clinic and cannot be generalised to the broader population. It was also noted that some of the sociodemographic questions were not answered. This may be due to the nature of elderly patients in answering questionnaires, who may be hesitant in disclosing their personal information such as income or expenses.

Conclusion

This study provided preliminary insights on patients' potential responses if any medicine charges or cost-sharing mechanism is proposed. It is recommended that governments review existing health services in both the public and private carefully and address all related matters prior to implementing a new healthcare financing system. Assessing the factors influencing the WTP may help the government to improve the medicine financing mechanism to protect the needed group from catastrophic health expenditure and enhance the fair utilisation of health care services provided to all for more equitable health care.

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Conflict of interest statement

This study is not funded by any source and the authors does not have any conflict of interest.

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