ORIGINAL ARTICLE

Antimicrobial Consumption and Resistance of Restricted Antibiotics in a Level III Government Hospital

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ABSTRACT

Objectives. The objectives of the study were to determine the antibiotic consumption of restricted antibiotics and to correlate this with resistance rate.

Methods. A retrospective review of pharmacy dispensing records was conducted in the adult internal medicine wards of a tertiary level teaching hospital in the Philippines between March 2019 to February 2020. Antibiotic consumption was determined using Defined Daily Dose (DDD) per 1000 patient-days (PD). Correlations between antibiotic consumption and antibiotic resistance of restricted antibiotics were done. Outcomes were compared between Ward 1 (with the presence of a unit-dose pharmacist) and Ward 3 (without a unit-dose pharmacist).

Results. Both wards showed decreasing trends of piperacillin-tazobactam consumption and increasing trends of ceftazidime consumption from quarter 1 to quarter 4. It was observed that levofloxacin was the most prescribed fluoroquinolone with the highest consumption recorded from March to May 2019 in Ward 3 of 350.2 DDD/1000 PD as compared with ciprofloxacin which has the highest consumption (23.3 DDD/1000 PD) during the period June to August 2019 in Ward 1. Antibiotic resistance of *Acinetobacter baumannii* against ciprofloxacin, levofloxacin, and piperacillin-tazobactam were statistically significantly different between the wards. In Ward 1, ciprofloxacin consumption was strongly positively correlated with *Escherichia coli* resistance (r = 0.90). In Ward 3, a significantly moderately positive association was observed for ceftazidime consumption and *A. baumannii* resistance (r = 0.61), positive correlation between piperacillin-tazobactam and *E. coli* resistance (r = 0.65), and a strong positive correlation in Ward 3 between levofloxacin and *Pseudomonas aeruginosa* resistance (r = 0.71).

Conclusion. The restriction and pre-authorization strategy of the AMS program has greatly contributed to the decrease in the consumption of almost all restricted antibiotics. This strategy has been helpful in minimizing unnecessary antibiotic use associated with inappropriate drug therapy. The success of the AMS program has been based on the collective efforts of the AMS team with the implementation of hospital policies, such as the AMS program, across the different sites in the hospital in order to achieve optimum patient health outcomes. It was noted that the resistance rates of *A. baumannii* against ciprofloxacin, levofloxacin, and piperacillin-tazobactam were higher in Ward 3 compared to Ward 1 which makes infections very difficult to treat which may result to prolonged hospital stay, increased health-care costs and increased mortality rate. This study has supported the involvement of pharmacists in the AMS team by conducting auditing activities that promote safe compliance of restricted antibiotic use among patients. Pharmacists can greatly participate on either prospective or retrospective review of antibiotic utilization and analyze trends of antibiotic consumption data to provide feedback to prescribing physicians on prescribing patterns and possible correlation with occurrence of antibiotic resistance.

Keywords: antibiotic consumption, antibiotic resistance, restricted antibiotics

** Prof. Abeleda and Dr. Peña shared first authorship for this manuscript.*

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INTRODUCTION

The rapid emergence of resistant bacterial infections is occurring worldwide, endangering the efficacy of antibiotics.[1] Antibiotic resistance happens when bacteria evolve and resist the effects of antibiotics which lead to higher medical costs, prolonged hospital stays, and increased mortality.[2] The emerging problem of antibiotic resistance not only interfere with the ability of antibiotics to treat infections but may also result to a broader societal and economic effects and may result to failure of achieving the Sustainable Development Goals developed by the United Nations.[3,4]

The acceleration of antimicrobial resistance (AMR) is caused by the misuse and overuse of antibiotics.[2] The WHO developed a Global Action Plan on AMR, including antibiotic resistance.[5,6] The WHO provided strategic and technical guidance on interventions to contain resistance which are directed towards prescribers and dispensers. One of the recommendations for intervention to prescribers and dispensers is to review both prescribing and dispensing practices to provide feedback on appropriate antibiotic prescribing. Researchers have recommended interventions to the hospital which include monitoring antibiotics usage, quantity prescribed and patterns of use, and inform prescribers about the results. It was also part of their recommendations to designate an effective Pharmacy and Therapeutics Committee to oversee antibiotic use in hospitals.[7] Pharmacists can play an active role in surveillance of antimicrobial consumption and resistance which are essential in determining the magnitude of AMR, help in establishing trends, and to further improve strategies to lessen the burden of antimicrobial resistance.[8]

Antimicrobial consumption data are collected using the Anatomical Therapeutic Chemical (ATC) classification system and Defined Daily Dose (DDD) methodology developed by the WHO Collaborating Centre for Drug Statistics Methodology.[9]

Philippine General Hospital (PGH) is a Level III government hospital administered and operated by the University of the Philippines Manila. It is the largest government hospital within Metro Manila with its 1,500-bed capacity. Since May 2016, the PGH Antimicrobial Stewardship (AMS) Program has been implemented within the hospital and has been organizing and providing training on AMS to other hospitals. The program is designed to enable antimicrobial prescriber (PGH physicians) as well as antimicrobial dispensers (PGH pharmacists) and practicing nurses, to use antimicrobial agents in the most rational, effective, efficient manner and eventually help curb antimicrobial resistance.

The WHO carried out a comprehensive review of antibiotics and classified antibiotics into Access, Watch, and Reserve (AWaRe) groups. The main goal is to reduce the use of Watch Group and Reserve Group antibiotics, the most crucial antibiotics for human medicine and are at higher risk of resistance, and increase the use of Access Group.[10] In PGH, the available restricted antibiotics under the watch group includes cefepime, ceftazidime, ciprofloxacin, ertapenem, levofloxacin, meropenem, piperacillin - tazobactam, and vancomycin. The restricted antibiotics that are under the reserve group includes colistin (polymyxin E) and polymyxin B. These antibiotics require PGH restricted antibiotic request form (also known as PGH Form No. P-370066) which should be completely accomplished by the physician and will be subjected for approval of Infectious Disease Section (IDS) fellow/consultant. The PGH, despite being known for providing AMS training to other private and government hospitals, lacks the data on the monitoring of its antibiotic consumption, despite the implementation of the AMS program in the institution. This was the first study that determined the antibiotic consumption of restricted antibiotics using DDD and correlated antibiotic consumption with resistance.

METHODS

In accordance with the Data Privacy Act of 2012 and its 2016 IRR, the principal investigator has complied with the institution's policies on handling patient information. Data collection started after securing the approval of UP Manila Research Ethics Board (UPMREB) and Extended Hospital Research Office (EHRO) of PGH. All the study team members have ensured the data privacy and patient's confidentiality by identifying each patient with subject-generated identification codes to be recorded in the data collection form. Only the members of the research team have accessed to the database all throughout the implementation of study.

A retrospective cross-sectional design was conducted between two wards under the Department of Medicine from March 2019 to February 2020. Since retrospective data collection was done manually by checking each patient's dispensing record, the principal investigator has opted to cover only one-year data. Both wards have a 50-bed capacity in PGH, a level III government hospital. This study determined and compared the antimicrobial consumption of drugs for systemic use (ATC group J01) specifically restricted antibiotics using the DDD per 1000 patient days.

Only Ward 5 (neurosciences ward) and Ward 1 (medicine ward) have a unit-dose pharmacist in the entire charity In-patient wards. The Department of Medicine specifically Ward 1 and Ward 3 were chosen because these were comparable based on the differences of medication distribution system. Ward 1 has a modified unit-dose drug distribution system (MUDDDS) with the participation of a unit-dose pharmacist. On the other hand, Ward 3 has an individual medication order system without a unit-dose pharmacist. The study also correlated antibiotic consumption of restricted antibiotics and antibiotic resistance rate of the top ten resistant microorganisms found in the Department of Medicine specifically Ward 1 and Ward 3.

Participants and Other Data Sources

The study included pharmacy dispensing records of charity in-patients who were admitted and transferred to the Department of Medicine specifically Ward 1 and Ward 3 from March 1, 2019, to February 29, 2020. Patients who were prescribed and dispensed with at least one dose of intravenous restricted antibiotics regardless of age, sex, and co-morbidities were included in the study.

Instrumentation

The CVR (content validity ratio), also known as Lawshe's method, was used to quantify content validity of the antibiotic consumption form. Five infectious disease pharmacists, who have undergone training on infectious diseases at University of the Philippines Manila, have been asked to evaluate the validity of the items in the data collection form using the evaluation sheet by indicating whether it is essential (item to be included in the form) or non-essential (item to be removed from the data collection form).

$$CVR = \frac{ne - (N/2)}{(N/2)}$$

The result was computed using the above formula. CVR stands for content validity ratio, *ne* pertains to the number of panel members indicating "essential," and *N* is the total number of panel members. The final evaluation to retain the item based on the CVR depends on the number of panels. In this study, for an item to be included, the CVR value per item should be 1.[11] Seven items had a CVR of less than 1 which are not included in the final data collection form.

Data Collection

The Open ERP (Enterprise Resource Planning) system was used to gather necessary data needed in the antibiotic consumption form. Data on antibiotic use were collected quarterly from March 2019 to February 2020 and antibiotic consumption data were expressed as DDD per 1000 patient-days. Data on the total number of units or vials were entered and analyzed using Antimicrobial Consumption Tool version 2019 developed by Arno Muller in 2018.

Antibiotic resistance (%) were gathered from the antibiogram of the Department of Medicine specifically Ward 1 and Ward 3 provided by the Hospital Infection Control Unit of the hospital. Correlations between antibiotic consumption and antibiotic resistance in each ward were determined for those with at least six (6) observation months or complete information on resistance rates from March 2019 to February 2020.

Data Processing and Analysis

Trend analysis of quarterly consumption of restricted antibiotics was used to analyze pattern of use of antibiotic consumption of restricted antibiotics. Data on antibiotic consumption was converted to DDD per 1000 patient-days. Independent t-test was used in the comparison of antibiotic consumption and comparison of resistance rates between Ward 1 and Ward 3. Pearson Correlation Coefficient was used to measure the strength of a correlation between antibiotic consumption and antibiotic resistance rates.

RESULTS

There were decreasing trends of piperacillin-tazobactam consumption on both wards (Figure 1A). Vancomycin consumption in Ward 1 showed a decreasing trend from March to February 2020 (Figure 1B). For cefepime, consumption spiked for both wards during December 2019 to February 2020 (Figure 1C). Ceftazidime consumption in both wards were observed to continuously increase from quarter 1 to quarter 4, with consumption slightly higher in Ward 3 compared to Ward 1 across all quarters (Figure 1D).

There was a sudden increase in ciprofloxacin consumption in Ward 1 during June to August 2019 but was of relatively same levels in the remaining quarters of the observation period, while consumption in Ward 3 dropped in the second and fourth quarters (Figure 2A). In this study, it was observed that levofloxacin was more prescribed with the highest consumption recorded during March to May 2019 in Ward 3 of 350.2 DDD/1000 PD as compared with ciprofloxacin which has the highest consumption during June to August 2019 in Ward 1 of 23.3 DDD/1000 PD (Figure 2B).

For ertapenem, consumption increased from March to November 2019 in both wards but shrank in December 2019 to February 2020 (Figure 2C). Ertapenem consumption was higher in Ward 1 in quarters 1, 2, and 4 than in Ward 3. High levels of consumption were recorded in Ward 1 and 3 for meropenem from March to November 2019 but declined in the fourth quarter of observation period (Figure 2D).

Colistin consumption was observed to decrease from quarter 1 through 4 in both wards, with greater consumption levels in Ward 1 compared to Ward 3 except in September to November 2019 (Figure 3A). Polymyxin B has an increasing trend of consumption from first quarter to third quarter of the study, however, consumption declined on the fourth quarter of the study (Figure 3B).

Antibiotic resistance of *Klebsiella pneumoniae* was highest against ceftazidime, with mean resistance of 67.2% in Ward 1 and 66.4% in Ward 3 (Table 1). However, antibiotic resistance was not statistically significantly different between the two wards.

Average antibiotic resistance of *A. baumannii* was generally higher in Ward 3 than in Ward 1 across all restricted antibiotics (Table 2). *A. baumannii* resistance to ciprofloxacin, levofloxacin, and piperacillin-tazobactam were statistically significantly different between two wards with Ward 3 having higher resistance compared to Ward 1.

Ciprofloxacin consumption in Ward 1 was significantly strongly positively correlated with *E. coli* resistance (Table 3). Meropenem consumption was weakly negatively associated with *E. coli* resistance.

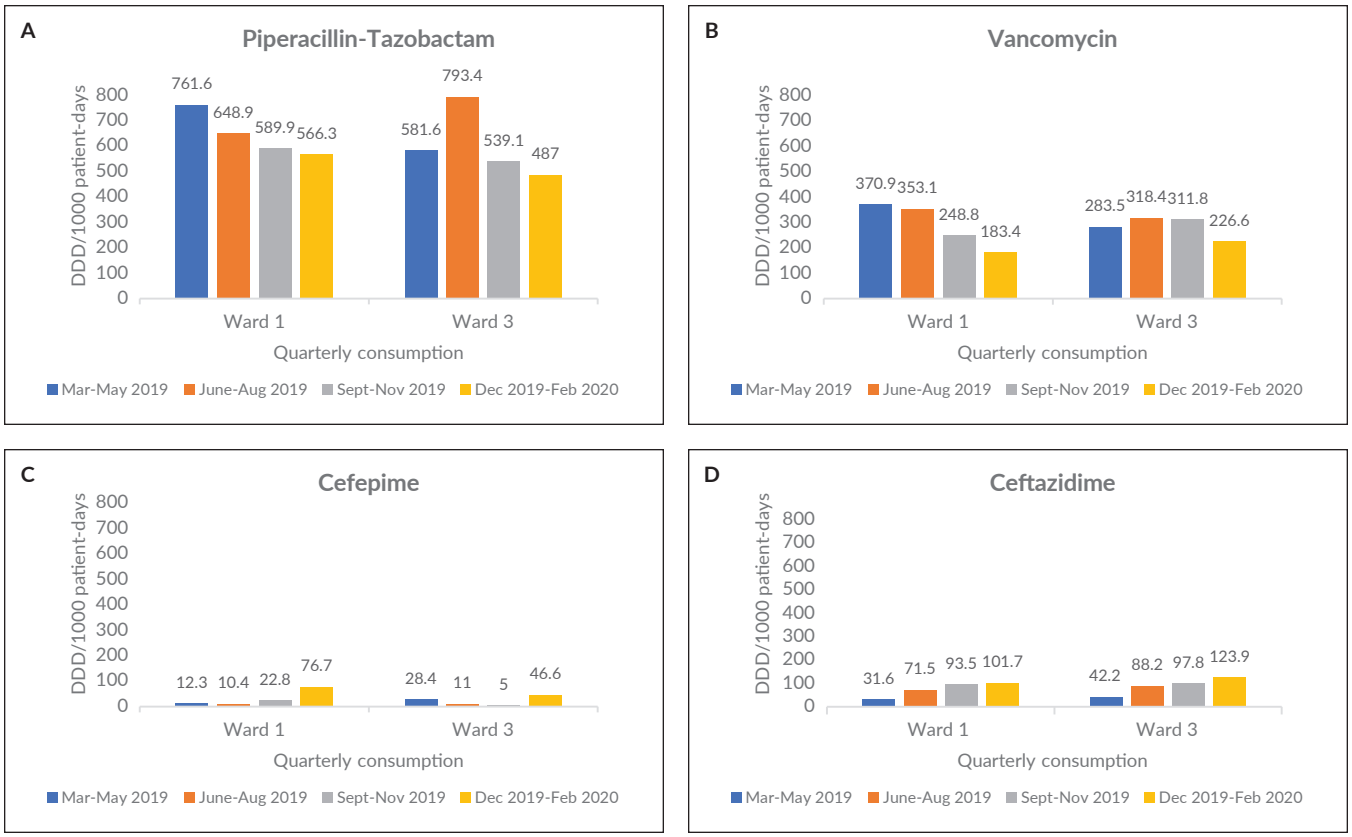

Figure 1. Quarterly consumption (DDD/1000 patient-days) of restricted antibiotics under watch group between Ward 1 and Ward 3 from March 2019 to February 2020.

Table 1. Antibiotic Resistance of *K. pneumoniae* against Selected Restricted Antibiotics in Ward 1 and Ward 3 from March 2019 to February 2020

Restricted antibiotics	Antibiotic resistance (%)⁺		*p*-value*
	Ward 1	Ward 3	
Cefepime	65.8 (60.4, 71.3)	65.8 (56.8, 74.8)	0.9909
Ceftazidime	67.2 (62.9, 71.5)	66.4 (56.6, 76.3)	0.8741
Ciprofloxacin	42.6 (32.9, 52.3)	47.4 (37.2, 57.6)	0.4594
Levofloxacin	41.3 (28.8, 53.9)	45.5 (33.8, 57.1)	0.5943
Meropenem	38 (26.7, 49.4)	42.1 (29.4, 54.7)	0.6045
Piperacillin-tazobactam	50.4 (39.3, 61.5)	55.9 (47.0, 65.0)	0.3980

⁺*95% CI are in parentheses; *Significant at p-value <0.05*

Table 2. Antibiotic Resistance of *A. baumannii* against Selected Restricted Antibiotics in Ward 1 and Ward 3 from March 2019 to February 2020

Restricted antibiotics	Antibiotic resistance (%)⁺		*p*-value*
	Ward 1	Ward 3	
Cefepime	76.2 (62.2, 90.2)	90 (86.1, 93.9)	0.0572
Ceftazidime	71.1 (59.9, 82.3)	77 (67.8, 86.3)	0.3768
Ciprofloxacin*	69.6 (56.0, 83.3)	87.5 (82.3, 92.8)	0.0173
Levofloxacin*	66.2 (53.8, 78.6)	83.6 (76.0, 91.2)	0.0165
Meropenem	76.5 (63.2, 89.9)	88.6 (83.6, 93.6)	0.0820
Piperacillin-tazobactam*	78.1 (66.4, 89.8)	91.5 (87.3, 95.8)	0.0328

⁺*95% CI are in parentheses; *Significant at p-value <0.05*

In Ward 1 (Table 4), a negative correlation was observed for cefepime and *A. baumannii* resistance which indicates no linear relationship that, as consumption decreases, the resistance rate increases and vice versa. Moreover, contrary from what was observed in Ward 3 (Table 5), a significantly moderately positive association was observed for ceftazidime consumption and *A. baumannii* resistance.

Ward 3 correlation between cefepime consumption and *P. aeruginosa* resistance was weakly negative (Table 6). Levofloxacin consumption was significantly moderately positively associated with *P. aeruginosa* resistance.

In Ward 3, there is moderately positive correlation between piperacillin-tazobactam consumption and *E. coli* resistance which is statistically significant (Table 7).

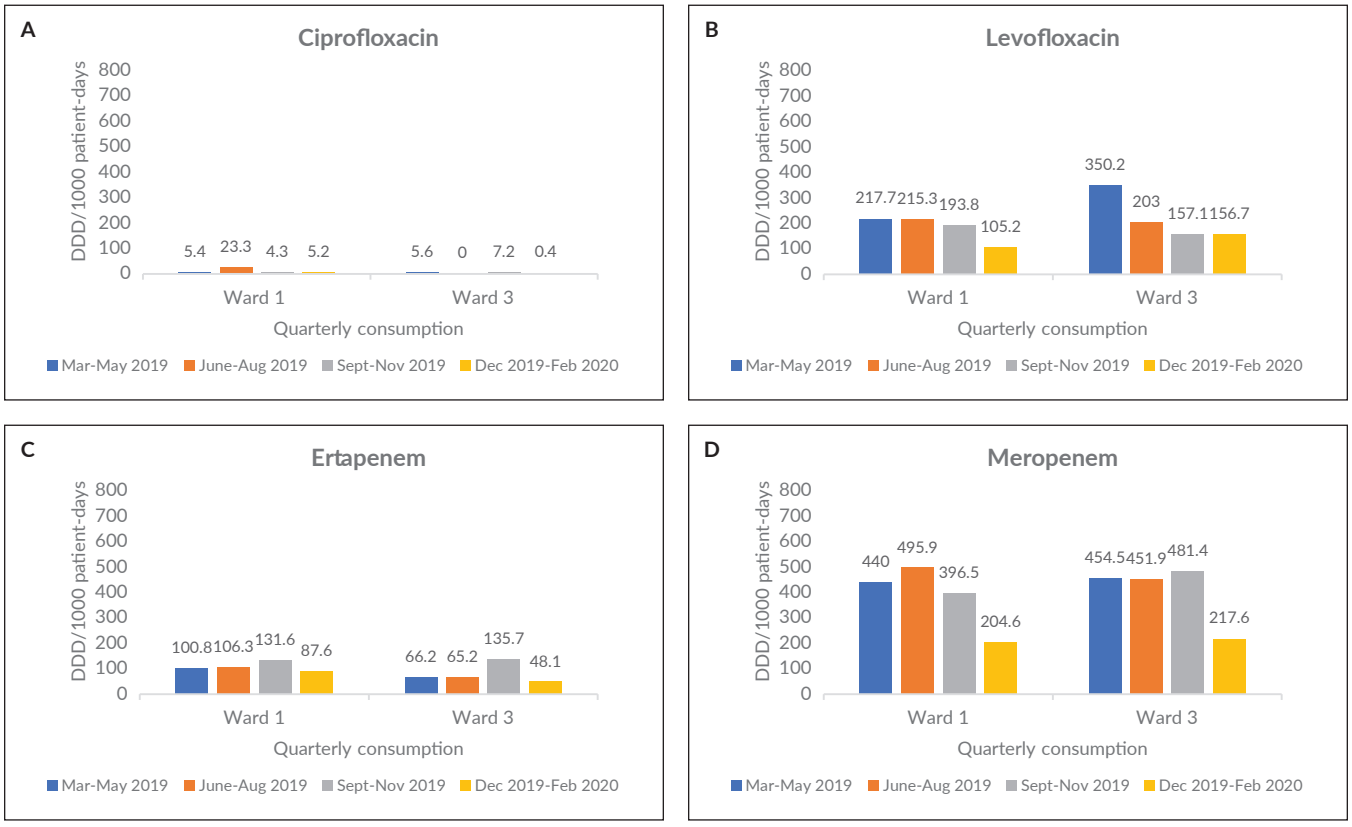

Figure 2. Quarterly consumption (DDD/1000 patient-days) of restricted antibiotics under watch group between Ward 1 and Ward 3 from March 2019 to February 2020.

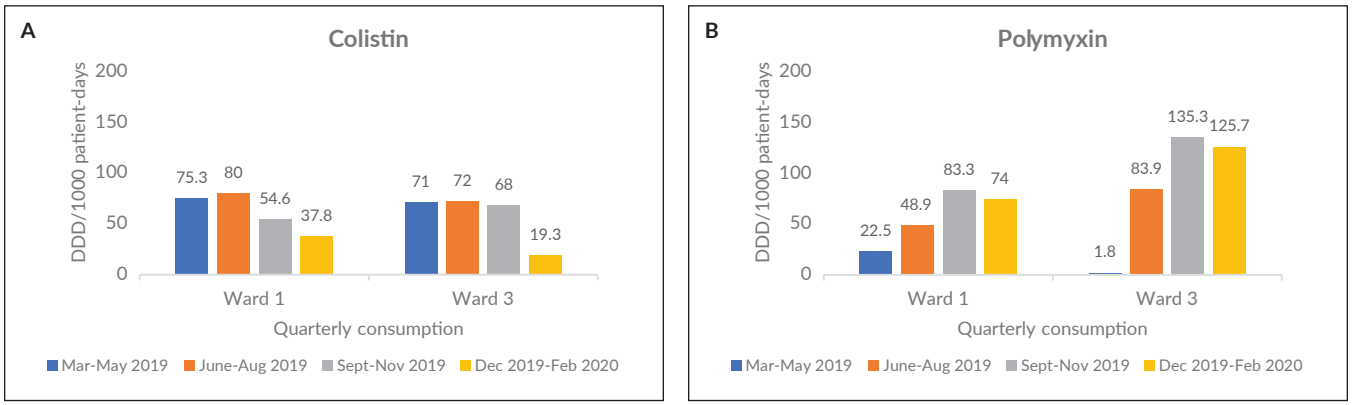

Figure 3. Quarterly consumption (DDD/1000 patient-days) of restricted antibiotics under reserve group between Ward 1 and Ward 3 from March 2019 to February 2020.

Table 3. Pearson's Correlation Coefficient of Antibiotic Consumption (DDD) and Antibiotic Resistance (%RR) of *E. coli* in Ward 1 from March 2019 to February 2020

Restricted antibiotics	Pearson's correlation (95% CI)	*p*-value*
Cefepime-	-0.16 (-0.72, 0.52)	0.6684
Ceftazidime-	-0.13 (-0.70, 0.54)	0.7146
Ciprofloxacin*++++	0.90 (0.34, 0.99)	0.0128
Levofloxacin+	0.21 (-0.49, 0.74)	0.5697
Meropenem--	-0.33 (-0.81, 0.43)	0.39
Piperacillin-tazobactam+	0.04 (-0.60, 0.65)	0.9077

**Significant at p-value <0.05*
+ negligible positive; ++ weakly positive; +++ moderately positive; ++++ strongly positive
- negligible negative; - - weakly negative; - - - moderately negative; - - - - strongly negative

Table 4. Pearson's Correlation of Antibiotic Consumption (DDD) and Antibiotic Resistance (%RR) of *A. baumannii* in Ward 1 from March 2019 to February 2020

Restricted antibiotics	Pearson's correlation (95% CI)	*p*-value*
Cefepime -	-0.16 (-0.72, 0.52)	0.6627
Ceftazidime +	0.07 (-0.59, 0.67)	0.8492
Ciprofloxacin +	0.08 (-0.78, 0.84)	0.8812
Levofloxacin+++	0.58 (-0.02, 0.88)	0.0597
Meropenem +	0.20 (-0.45, 0.72)	0.5456
Piperacillin-tazobactam +	0.10 (-0.54, 0.66)	0.7809

**Significant at p-value <0.05*
+ negligible positive; ++ weakly positive; +++ moderately positive; ++++ strongly positive
- negligible negative; - - weakly negative; - - - moderately negative; - - - - strongly negative

Table 5. Pearson's Correlation of Antibiotic Consumption (DDD) and Antibiotic Resistance (%RR) of *A. baumannii* in Ward 3 from March 2019 to February 2020

Restricted antibiotics	Pearson's correlation (95% CI)	*p*-value*
Cefepime -	-0.19 (-0.80, 0.36)	0.57
Ceftazidime *+++	0.61 (0.01, 0.86)	0.05
Levofloxacin -	-0.19 (-0.71, 0.46)	0.58
Meropenem -	-0.06 (-0.64, 0.56)	0.87
Piperacillin-tazobactam +	0.17 (-0.48, 0.70)	0.62

**Significant at p-value <0.05*
+ negligible positive; ++ weakly positive; +++ moderately positive; ++++ strongly positive
- negligible negative; - - weakly negative; - - - moderately negative; - - - - strongly negative

Table 6. Pearson's Correlation of Antibiotic Consumption (DDD) and Antibiotic Resistance (%RR) of *P. aeruginosa* in Ward 3 from March 2019 to February 2020

Restricted antibiotics	Pearson's correlation (95% CI)	*p*-value*
Cefepime - -	-0.48 (-0.89, 0.34)	0.225
Ceftazidime +	0.17 (-0.52, 0.72)	0.647
Levofloxacin * +++	0.71 (0.01, 0.94)	0.049
Meropenem +	0.24 (-0.42, 0.74)	0.474

**Significant at p-value <0.05*
+ negligible positive; ++ weakly positive; +++ moderately positive; ++++ strongly positive
- negligible negative; - - weakly negative; - - - moderately negative; - - - - strongly negative

Table 7. Pearson's Correlation of Antibiotic Consumption (DDD) and Antibiotic Resistance (%RR) of *E. coli* in Ward 3 from March 2019 to February 2020

Restricted antibiotics	Pearson's correlation (95% CI)	*p*-value*
Cefepime - - -	-0.51 (-0.86, 0.18)	0.132
Ceftazidime - - -	-0.51 (-0.86, 0.17)	0.129
Levofloxacin - - -	-0.65 (-0.92, 0.02)	0.057
Meropenem + +	0.38 (-0.36, 0.84)	0.306
Piperacillin-tazobactam * +++	0.65 (0.04, 0.91)	0.042

**Significant at p-value <0.05*
+ negligible positive; ++ weakly positive; +++ moderately positive; ++++ strongly positive
- negligible negative; - - weakly negative; - - - moderately negative; - - - - strongly negative

DISCUSSION

In general, the result of the study has provided essential information in evaluating AMR containment interventions such as the AMS program. Data can be shared with the AMS team of hospital and relevant information can be further cascaded to other institutions and to Department of Health to track the progress of AMS interventions in reducing antibiotic consumption and resistance.

The decreasing trends in consumption of piperacillin-tazobactam showed a decreased use of piperacillin-tazobactam among patients. Based on the antibiogram result, gram-negative bacteria were frequently isolated from patients' samples. Decreasing trend of vancomycin consumption may be associated with its inactivity against gram-negative bacteria, hence, the decreased in usage. The increase in the antibiotic consumption of ceftazidime must be monitored as it has the highest resistance recorded against *K. pneumoniae* in this study. In the study of Rice et al.,[12] the highest rates of resistance occurred in wards where ceftazidime was administered most frequently.

Although levofloxacin was the preferred fluoroquinolone compared with ciprofloxacin, its consumption fell in both wards from quarter 1 through quarter 4 due to decreased use

in the wards which could mean that prevalence of infection does not require its use. Levofloxacin and ciprofloxacin are both recommended for clinical application in UTIs and, though commonly prescribed, there's no conclusion on the comparative merit of the either one. Levofloxacin shows advantage over ciprofloxacin in terms of efficacy, disease reoccurrence, and adverse event.[13] On the contrary, microbiology evidence shows that the uropathogen is more sensitive to ciprofloxacin.[14,15]

Ciprofloxacin is a second-generation fluoroquinolone which exhibit improved intracellular penetration and broadened coverage, which includes *Enterobacteriaceae*, *P. aeruginosa*, *Haemophilus influenzae*, *Neisseria spp., Chlamydia spp., and Legionella spp.* On the other hand, levofloxacin is a third-generation fluoroquinolone which maintain the bacterial spectrum of second-generation agents, with improved activity against *Streptococcus spp*., including *Streptococcus pneumoniae, methicillin-susceptible Staphylococcus aureus, Stenotrophomonas maltophilia,* and *Mycobacterium spp.*[16] Higher consumption for levofloxacin may be due to its wider coverage as compared with ciprofloxacin.

Ertapenem consumption was three times lower as compared with meropenem consumption because the spectrum of activity of ertapenem is more limited primarily because it lacks activity against *P. aeruginosa* and *Acinetobacter spp*.[17] It was observed that meropenem was the most consumed carbapenem antibiotic as compared with ertapenem. High consumption may be attributed to its activity against Gram-positive bacteria and Gram-negative bacteria, including extended-spectrum beta-lactamase-producing Enterobacteriaceae, *P. aeruginosa,* and *Acinetobacter spp*.[18]

Colistin consumption decreases as polymyxin consumption increases. Internal Medicine residents have opted to use polymyxin as polypeptide antibiotic than colistin. Polymyxin B is administered parenterally in its active form, while colistin is administered parenterally as an inactive prodrug, colistimethate.[19] In addition, published clinical studies suggest that polymyxin B is less nephrotoxic than colistin. For these reasons, polymyxin B has become the predominant polymyxin used in many health centers and hospital.[20]

In the study of Yadav et al.,[21] it was found that 99.4% of *A. baumannii* were resistant to ceftazidime and cefepime, 95% to piperacillin-tazobactam and ciprofloxacin, 89.4% resistant to meropenem. This is in contrast with the present study findings where in the recorded resistance rate to ceftazidime (71.1% in Ward 1 and 77% in Ward 3) and piperacillin-tazobactam (78.1% in Ward 1 and 91.5% in Ward 3) were lower. The study of Yadav et al. included pediatric patients which could have influenced why the result appeared to be higher compared to the present study that covered only adult patient population.

Based on the study findings, higher resistances of *A. baumannii* to ciprofloxacin, levofloxacin, and piperacillin-tazobactam in Ward 3 were statistically significantly different compared to Ward 1.The unit-dose pharmacist helped in ensuring that restricted antibiotics were given on time and there were no missed doses to prevent antibiotic resistance. The pharmacist's presence had contributed to the result that Ward 1 had lower resistance rates on *A. baumannii* compared to Ward 3.

The result of the present study is similar with the study of Lai et al.,[22] wherein the consumption of fluoroquinolones was positively correlated with the resistance rate of *P. aeruginosa*. This means that as the consumption of fluoroquinolones increases, the resistance to *P. aeruginosa* also increases. In the same study of Lai et al.,[22] the use of piperacillin-tazobactam was positively correlated with the prevalence of piperacillin-tazobactam-resistant *E. coli*. This is similar with the present study findings which shows that as piperacillin-tazobactam consumption increases, *E. coli* resistance also increases. The result of the present study is similar with the study of Lai et al.,[22] wherein there was a positive correlation between increase of fluoroquinolones and emergence of ciprofloxacin-resistant *E. coli* based on 2007 to 2016 data. This means that ciprofloxacin consumption tends to be associated with *E. coli* resistance over the years.

Both wards showed decreasing trends in consumption of watch antibiotics except for ceftazidime which could mean that the antimicrobial stewardship program of the hospital is serving its purpose in eliminating unnecessary use of restricted antibiotics.

Limitations of the Study

ATC/DDD methodologies are used to compare drug consumption among institutions, regions, and countries. However, DDD does not automatically reflect recommended or average prescribed dose. Instead, it is only a technical unit. It is referred to as the assumed average maintenance dose per day for a drug used for its main indication in adults.

Patient demographics such as age and sex were confounding variables in the study. As a person gets older, the greater is the risk of having infections due to comorbidities. Previous studies have found that male patients are more at risk of developing infections that would require the use of restricted antibiotics. In this study, the effect of these confounders was minimized by including male and female patients aged 18 to 95.

Both medicine wards have the same rotating IM residents who handle the patients. Both wards cater patients who have hypertensive cardiovascular disease, cutaneous and subcutaneous infectious, heart failure, chronic kidney disease, septic shock, diabetes, and hospital acquired pneumonia.

The study had several limitations. First, the scope of the study included only one-year data which had led to sparse data in terms of antibiotic consumption and resistance. Second, the measurement of antibiotic use was based on the dispensing record of the pharmacy, not based on those actually consumed by admitted patients. Findings have limited extent of generalizability to other healthcare settings.

Investigation of other possible reasons for the increase and decrease of antibiotic consumption was likewise limited because there was no direct access to patient chart. Assessment of clinical practice against set protocols and guidelines was beyond the scope of this study.

CONCLUSION

The restriction and pre-authorization strategy of the AMS program has greatly contributed to the decrease in the consumption of almost all restricted antibiotics. This strategy has been helpful in minimizing unnecessary antibiotic use associated with inappropriate drug therapy. The success of the AMS program has been based on the collective efforts of the AMS team with the implementation of hospital policies, such as the AMS program, across the different sites in the hospital in order to achieve optimum patient health outcomes.

There was no significant difference in terms of resistance rates of the top 10 most commonly isolated bacteria. However, it was noted that the resistance rates of *A. baumannii* against ciprofloxacin, levofloxacin, and piperacillin-tazobactam were higher in Ward 3 compared to Ward 1 which makes infections very difficult to treat which may result to prolonged hospital stay, increased health-care costs, and increased mortality rate. There were significant positive correlations found between antibiotic consumption and antibiotic resistance which is why monitoring antibiotic consumption is important in controlling antibiotic resistance. Therefore, each hospital should monitor antibiotic consumption and further explore its relationship with resistance rate of each bacterium.

This study has supported the involvement of pharmacists in the AMS team by conducting auditing activities that promote safe compliance of restricted antibiotic use among patients. Pharmacists can greatly participate on either prospective or retrospective review of antibiotic utilization and analyze trends of antibiotic consumption data to provide feedback to prescribing physicians on prescribing patterns and possible correlation with occurrence of antibiotic resistance. Data in the collection and management of antibiotics, monitoring of use, and analyses of gaps for pharmacist-led interventions.

With proper support and resources, a prospective study would be ideal in order for pharmacists to participate in antimicrobial stewardship interventions such as evaluation of antibiotic usage, adjustment on the dose for renal dysfunction, switching from parenteral to oral, de-escalation of empiric to narrow spectrum based on antibiogram result, escalation of empiric narrow spectrum to empiric broad spectrum antibiotic based on clinical deterioration of the patient and laboratory indicators as recommended by Boyles et al.[23] It would also be better for future researchers to gain access to patient chart to investigate possible reasons for the increase and decrease of antibiotic consumption at the patient level.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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REFERENCES

1. Golkar Z, Bagasra O, Pace DG. Bacteriophage therapy: a potential solution for the antibiotic resistance crisis. J Infect Dev Ctries. 2014 Feb;8(2):129–36. doi: 10.3855/jidc.3573. PMID: 24518621.
2. World Health Organization. Antibiotic resistance [Internet]. 2020 [cited 2021 Jun 10]. Available from: https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance
3. World Bank. Drug-Resistant Infections: A Threat to Our Economic Future [Internet]. World Bank. [cited 2021 Aug 18]. Available from: https://www.worldbank.org/en/topic/health/publication/drug-resistant-infections-a-threat-to-our-economic-future
4. World Health Organization. Regional Office for Europe. The fight against antimicrobial resistance is closely linked to the Sustainable Development Goals [Internet]. World Health Organization. Regional Office for Europe. 2020 [cited 2021 Aug 7]. Available from: https://apps.who.int/iris/handle/10665/337519
5. World Health Organization, Food and Agriculture Organization of the United Nations, World Organisation for Animal Health. Monitoring and evaluation of the global action plan on antimicrobial resistance: framework and recommended indicators [Internet]. World Health Organization. 2019 [cited 2021 Oct 1]. 32 p. Available from: https://apps.who.int/iris/handle/10665/325006
6. World Health Organization. Global action plan on antimicrobial resistance [Internet]. World Health Organization. 2015 [cited 2021 Jul 20]. 28 p. Available from: https://apps.who.int/iris/handle/10665/193736
7. World Health Organization. Anti-Infective Drug Resistance Surveillance and Containment Team. WHO global strategy for containment of antimicrobial resistance [Internet]. World Health Organization. 2001 [cited 2021 Apr 20]. Available from: https://apps.who.int/iris/handle/10665/66860
8. International Pharmaceutical Federation. Fighting Antimicrobial Resistance: The Contribution of Pharmacists [Internet]. International Pharmaceutical Federation. 2015 [cited 2021 May 21]. Available from: https://www.fip.org/file/163
9. World Health Organization. Defined Daily Dose (DDD): Definition and general considerations [Internet]. [cited 2021 Sep 18]. Available from: https://www.who.int/tools/atc-ddd-toolkit/about-ddd
10. WHO Access, Watch, Reserve (AWaRe) classification of antibiotics for evaluation and monitoring of use [Internet]. Geneva: World Health Organization. 2021 [cited 2020 July 10] (WHO/HMP/HPS/EML/2021.04). Licence: CC BY-NC-SA 3.0 IGO.
11. Taherdoost H. Validity and reliability of the research instrument; How to test the validation of a questionnaire/survey in a research. Int J Acad Res Manag. 2016; 5(3):28-36. doi: 10.2139/ssrn.3205040.

12. Rice LB, Eckstein EC, DeVente J, Shlaes DM. Ceftazidime-resistant Klebsiella pneumoniae isolates recovered at the Cleveland Department of Veterans Affairs Medical Center. Clin Infect Dis. 1996 Jul;23(1): 118-24. doi: 10.1093/clinids/23.1.118. PMID: 8816140.
13. Zhang ZC, Jin FS, Liu DM, Shen ZJ, Sun YH, Guo YL. Safety and efficacy of levofloxacin versus ciprofloxacin for the treatment of chronic bacterial prostatitis in Chinese patients. Asian J Androl. 2012 Nov;14(6):870-4. doi: 10.1038/aja.2012.48. PMID: 22864282; PMCID: PMC3720113.
14. Afriyie DK, Adu LB, Dzradosi M, Amponsah SK, Ohene-Manu P, Manu-Ofei F. Comparative in vitro activity of ciprofloxacin and levofloxacin against isolated uropathogens in Ghana: a pilot study. Pan Afr Med J. 2018 Jul 5;30:194. doi: 10.11604/pamj.2018.30.194.15457. PMID: 30455823; PMCID: PMC6235466.
15. Humphries RM, Hindler JA, Shaffer K, Campeau SA. Evaluation of ciprofloxacin and levofloxacin disk diffusion and Etest using the 2019 Enterobacteriaceae CLSI breakpoints. J Clin Microbiol. 2019 Feb;57(3):e01797-18. doi: 10.1128/JCM.01797-18. PMID: 30567744; PMCID: PMC6425192.
16. Whalen K, Feild C, Radhakrishnan R. Lippincott Illustrated Reviews: Pharmacology. 7th edition. Philadelphia: Wolters Kluwer; 2019.
17. Zhanel GG, Wiebe R, Dilay L, Thomson K, Rubinstein E, Hoban DJ, et al. Comparative review of the carbapenems. Drugs. 2007; 67(7):1027-52. doi: 10.2165/00003495-200767070-00006. PMID: 17488146.
18. Rattanaumpawan P, Werarak P, Jitmuang A, Kiratisin P, Thamlikitkul V. Efficacy and safety of de-escalation therapy to ertapenem for treatment of infections caused by extended-spectrum-β-lactamase-producing Enterobacteriaceae: an open-label randomized controlled trial. BMC Infect Dis. 2017 Mar;17(1):183. doi: 10.1186/s12879-017-2284-1. PMID: 28249572; PMCID: PMC5333449.
19. Cai Y, Lee W, Kwa AL. Polymyxin B versus colistin: an update. Expert Rev Anti Infect Ther. 2015;13(12):1481-97. doi: 10.1586/14787210.2015.1093933. PMID: 26488563.
20. Grégoire N, Aranzana-Climent V, Magréault S, Marchand S, Couet W. Clinical pharmacokinetics and pharmacodynamics of colistin. Clin Pharmacokinet. 2017 Dec;56(12):1441-60. doi: 10.1007/s40262-017-0561-1. PMID: 28550595.
21. Yadav SK, Bhujel R, Hamal P, Mishra SK, Sharma S, Sherchand JB. Burden of multidrug-resistant Acinetobacter baumannii infection in hospitalized patients in a tertiary care hospital of Nepal. Infect Drug Resist. 2020 Mar;13:725-32. doi: 10.2147/IDR.S239514. PMID: 32184634; PMCID: PMC7061726.
22. Lai CC, Wang CY, Chu CC, Tan CK, Lu CL, Lee YC et al. Correlation between antibiotic consumption and resistance of Gram-negative bacteria causing healthcare-associated infections at a university hospital in Taiwan from 2000 to 2009. J Antimicrob Chemother. 2011 Jun;66(6):1374-82. doi: 10.1093/jac/dkr103. PMID: 21436153.
23. Boyles TH, Whitelaw A, Bamford C, Moodley M, Bonorchis K, Morris V, et al. Antibiotic stewardship ward rounds and a dedicated prescription chart reduce antibiotic consumption and pharmacy costs without affecting inpatient mortality or re-admission rates. PLoS One. 2013 Dec 9;8(12):e79747. doi: 10.1371/journal.pone.0079747. PMID: 24348995; PMCID: PMC3857167.