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Point Prevalence Survey on Antibiotic Use and Class-1 Integron Associated Antibiotic Resistance In No (1) DSGH, Yangon

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ABSTRACT: Antimicrobial resistance is becoming a global health emergency. Likewise, multidrug resistance of gram-negative bacteria also has a high impact on public health. This cross-sectional study aimed to study antibiotic prescription patterns and class-1 integron-associated antibiotic resistance among gram-negative bacteria in No (1) Defence Services General Hospital, Yangon. The research was conducted by modifying the WHO PPS methodology. All eligible patients who were prescribed antibiotics on the day of the survey were investigated. Among the participants whose culture samples were sent to the laboratory, gram-negative bacterial culture samples undergone the class 1 integron test. There were 441 patients from 12 eligible wards with a total of 781 prescriptions in the study in January and July of 2020. The leading indication was surgical prophylaxis 257 (32.91%). Cephalosporins and Penicillins were mostly prescribed antibiotic classes. Among bacterial culture, (52.31%) were multidrug-resistant, and (47.69%) were gram-negative. Class 1 integron positivity and rate of multidrug resistance among GNB were (54.84%) and (90.32%). Class 1 integron positivity among multidrug resistance was (60.71%). There was no statistically significant association between class 1 integron and multidrug resistance in this study. Three and more antibiotic prescriptions, surgical prophylaxis, and old age group were positively associated with multi-drug resistance with (AOR=8.9, 95% CI; 2.3-34.2), (AOR=21.1, 95% CI; 2.1-210.0), and (AOR=4.6, 95%CI; 1.2-17.2) respectively. Antibiotic policy and standard treatment guidelines for the tertiary military hospital should be developed while surveillance of antibiotic resistance must be performed simultaneously.

KEYWORDS: Antimicrobial resistance, class-1 integron, PPS methodology, gram-negative bacteria

1. INTRODUCTION

Sir Alexander Fleming discovered penicillin in 1928, and this discovery remodeled medical practice. It still stands as the most powerful life-saving intervention by saving millions of lives (Maugeri et al., 2019). People once believed that the discovery of antibiotics could prevent and control nearly all kinds of infections. Despite that, the main prime of death is still infections in the evolving world (Kapoor et al., 2017). World Health Organization (WHO) endorsed the antimicrobial stewardship (AMS) initiatives to monitor antimicrobial usage and address the burden of antimicrobial resistance (AMR) (WHO, 2015). Healthcare-associated infections (HAIs) and antimicrobial resistance (AMR) are notorious threats in healthcare.

There are various mechanisms involved in antimicrobial resistance among the bacterial isolate, the acquisition of resistance genes by horizontal transfer mediated by integron play a crucial role. There are many classes of integron has been described in bacteria isolates, class 1 integron has been found to be the most prevalence in gram negative bacterial isolates (Kaushik et al., 2018).

The prevalence of integron positivity among multidrug-resistant organisms was studied in some Myanmar studies which revealed that all multidrug-resistant Klebsiella species from Thu et al.2021, and 95% of multidrug-resistant Pseudomonas species from Win et al. 2021, were positive for class 1 integron. The association between the presence of class 1 integron and multidrug resistance was statistically significant in a study conducted by Win et al 2021.

Continuous data collection on antibiotic prescribing is not feasible because of the high workload and limited resources for typical monitoring. To overcome such an obstacle, an alternative way is to collect data at a specific point in time, by using the point prevalence survey (PPS) methodology. PPS on antibiotic use is already utilized in hospitals around the world (WHO, 2018). The present study aims to identify the prescription pattern of antibiotics in tertiary-level hospitals by using the WHO Point Prevalence Survey methodology.

2. RESEARCH METHODOLOGY

It was a hospital and laboratory based descriptive study at selected tertiary hospitals. All wards, patients, and antibiotics that fulfilled the inclusion criteria of PPS were selected. According to limited resources, time, and the COVID-19 pandemic, all patients who fulfilled the inclusion criteria were included in the study. The study was carried out in two points of time, the first one from 1st to 21st January and the second period from 1st to 21st July of 2020.

The study was carried out in the following procedures. Firstly, a point prevalence survey on antibiotic use was conducted. After that, the participants whose clinical specimens were sent to the laboratory for culture and sensitivity testing were chosen. Then, the specimen with positive growth for gram-negative bacilli was proceeded to detect the presence of mobile genetic elements class 1 integron gene. For the fear of dropout, human error, and data collection and entry error, the addition of 10 percent to the minimum required sample size resulting in 410 participants were collected to study.

2.1 Gram Negative Bacteria Identification and Antimicrobial Susceptibility Testing

All gram-negative bacteria isolated from clinical samples involved in PPS were recruited in this study. Gram negative bacteria identification and antimicrobial susceptibility testing of isolated organisms were assessed by VITEK 2 Compact Automated Microbiology Analyzer.

2.2 Class 1 Integron Gene Detection by Polymerase Chain Reaction

Primers (Int1F 5′-3′ AAGGATCGGGCCTTGATGTT and Int1R 5′-3′ CAGCGCATCAAGCGGTGAGC) 471bp were used. The reaction mixture was prepared using 2.5 μl of 10X ThermoPol Reaction Buffer, 0.5 μl of 10mM dNTPs, 0.5 μl of 10 μM forward primer, 0.5 μl of 10 μM reverse primer, 0.125 μl (0.625 U) of Taq DNA Polymerase, Template DNA 2 μl and add 18.875 μl of Nuclease free water. The samples were amplified in Applied Biosystem 7500 Fast Thermocycler instrument (Thermofisher Scientific, USA). Cycling program was as follows: preincubation at 94˚C for 5 min followed by 30 cycles of denaturation at 94˚C for 30 sec, annealing at 56˚C for 30 sec, extension at 72˚C for 30 sec and final extension at 72˚C for 7 min. Then, PCR products were separated by gel electrophoresis on 1.5 % agarose gels and were visualized under UV light.

Ethical considerations

The research proposal was submitted to and approved by the Ethical Review Committee, Defence Services Medical Academy. Ethical clearance will be followed by the guidance of the Department of Preventive and Social Medicine and the Academic Board of Studies, Defence Services Medical Academy.

3. RESULTS

The study was carried out in No (1) DSGH in 2020 with two points of time, the first one from 1st to 21st of January and the second one from 1st to 21st of July. Among the eligible wards, 441 patients met the study inclusion criteria and underwent the point prevalence survey. Among the total 781 antibiotics prescription, 257 (32.91%) are indicated for surgical prophylaxis, community-acquired infection is 162 (21.13%), 98 (12.55%) are prescribed according to the indication of medical prophylaxis, and nine indications (1.15%) is prescribed for a hospital-associated infection. Other indications (indication for minor injuries, illness, and nonspecific indication reason) are 252 (32.27%) (Figure-1).

Among the overall prescriptions, Cephalosporins are the most prescribing antibiotic class 261 out of 781 (33.42%), followed by Penicillins (19.85%) and Fluoroquinolones (17.93%). Cephalosporins are the most prescribed antibiotic class in all prescribing indications with data of 35.02 % for surgical prophylaxis, 33.33 % for other indication, 33.94% for community-acquired infections, 28.57% for medical prophylaxis, and 33.33% of hospital-associated infections.

In the present study, culture samples from 65 study participants (14.74 %) are taken and sent for culture and sensitivity testing. Nearly half, 31 out of 65 (47.69 %) of the culture samples sent to the laboratory are gram-negative microorganisms and the rest of the culture samples reveal gram-positive bacteria and yeast.

Among the 65 positive growth culture samples, over half, 34 out of 65, (52.31 %) are multi-drug-resistant while the rest of the samples, 31 out of 65 (47.69 %) are non-multi-drug resistant. The table (1) provides the gram-negative bacterial pathogens isolated from the study participants. Klebsiella pneumonia is the most common microorganism, 14 out of 31 (45.16 %) and Pseudomonas pudida is the less common one, one out of 31 (3.23 %).

Among the 31 gram-negative bacteria, over ninety percent, 28 (90.32 %) reveal multi-drug resistance while a tiny minority 3 out of 31 (9.68 %) show non-MDR. Detection of class 1 integron gene in isolated gram-negative bacteria was proceeded by polymerase chain reaction (PCR). Class 1 integron was detected over half of gram-negative bacteria, 17 out of 31 (54.84 %) are positive for the class 1 integron gene while the remaining 14 (45.16 %) are negative for the class 1 integron gene.

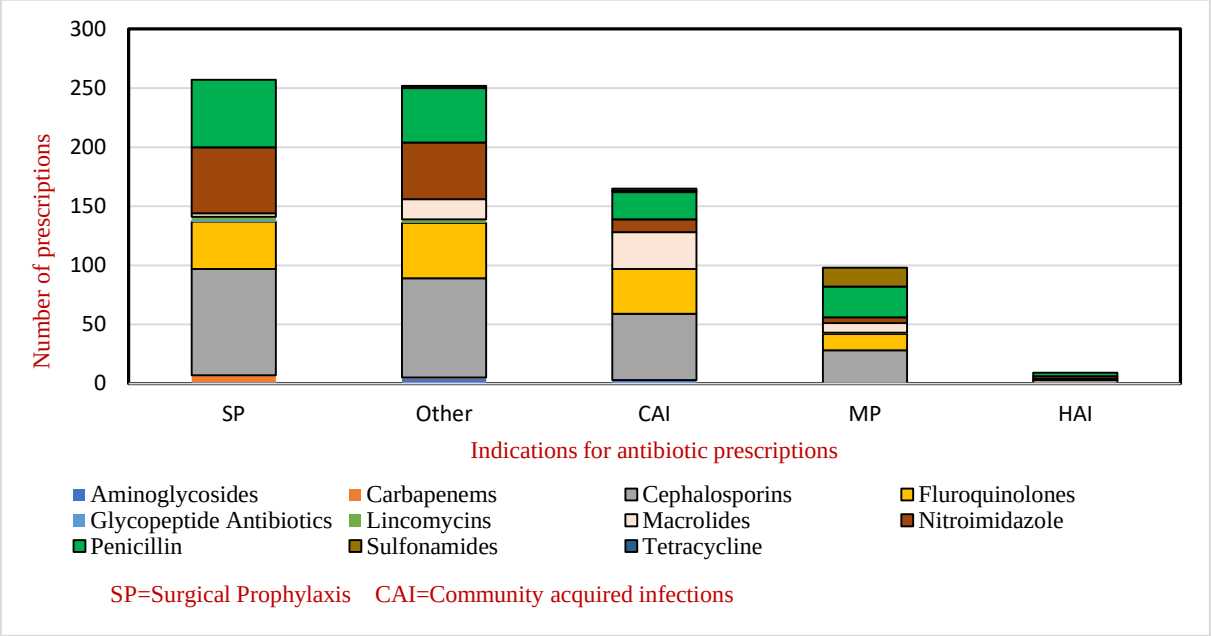

Figure 1. Antibiotic classes among prescriptions

Table 1. Gram-negative bacterial pathogens isolated from the study participants.

No.	Culture results	Number	Percentage
1	Klebsiella pneumoniae	14	45.16
2	Pseudomonas aeruginosa	7	22.58
3	Klebsiella oxytoca	4	12.90
4	Escherichia coli	3	9.68
5	Other gram-negative	2	6.45
6	Pseudomonas pudida	1	3.23
Total		31	100.00

The association between antibiotic resistance and the presence of class 1 integron

The proportion of class 1 integron positivity among MDR was 60.71%. The association between class 1 integron and multidrug resistance is calculated in the table (2). Fisher's exact test showed that there is no statistically significant association between class 1 integron and multidrug resistance.

Table 2. Association between multidrug-resistance and presence of class 1 integron among isolated gram-negative bacteria

No.	Class 1 Integron and multi-drug resistance		Multi-drug-resistant		Total
			resistant	no resistant	
1	Class 1 Integron	Positive	17 (60.71%)	0 (0.00%)	17 (54.84%)
2		Negative	11 (39.29%)	3(100.00%)	14 (45.16%)
Total			28 (100.00%)	3(100.00%)	31(100.00%)

X^2 (1, n=31) = 4.033, p = 0.081

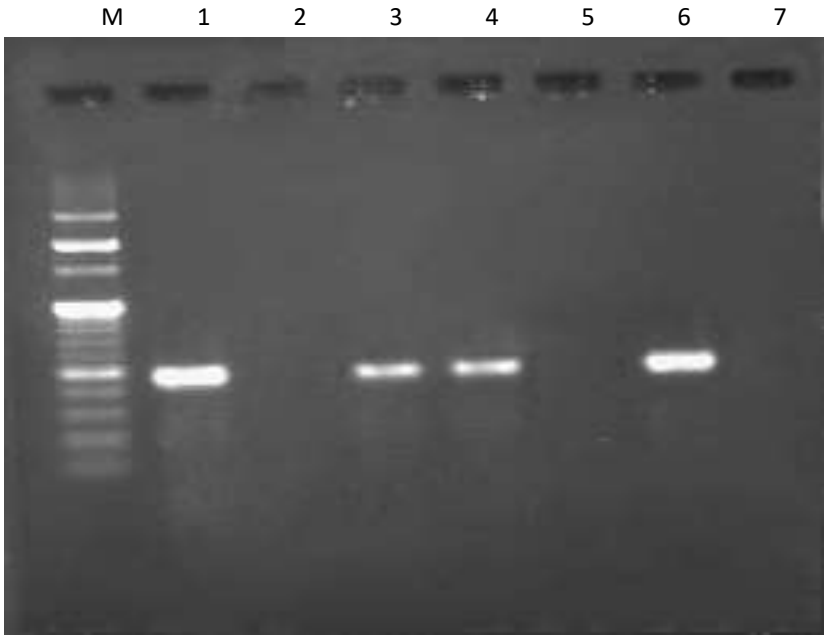

Plate (1) Detection of class 1 integron gene in bacteria species by PCR

(Lane M - 100bp DNA ladder, Lane 1,3,4,6 - Sample positive for int1 gene at 471 bp, Lane 2 and 5- Sample negative, Lane 7- No template control)

Table 3. Odds ratio (OR) and 95% confidence interval (CI) for multidrug-resistant among the study participants who underwent culture and sensitivity testing (n=65)

Variable	Odds ratio	95 % CI	p-value
Number of antibiotics less than 3 3 and above	1 4.69	1.53 – 14.32	0.007
Surgical prophylaxis No Yes	1 12.50	1.49 -104.61	0.020
Age group 50 years and below 51 years and above	1 3.37	1.19 – 9.54	0.022
Gender Male Female	1 2.58	0.84 - 7.97	0.100
Recent TB infection No Yes	1 6.43	0.73 – 56.80	0.094
Recent infections (Malaria/TB/HIV) No Yes	1 6.43	0.73 – 56.80	0.094

Bivariate analysis was done between MDR and six possible influencing factors on MDR and there are only three variables that showed statistically significant results. Prescription of antibiotics 3 and above is 4.69 times higher to be multidrug resistant than prescription of antibiotics less than or equal to 2 (OR=4.69, 95% CI; 1.53 – 14.32). Surgical prophylaxis indication is 12.50 times higher to be multidrug resistant than other prescribing indications (OR=12.50, 95% CI; 1.49 -104.61). Fifty-one years and above age group is 3.37 times higher to be resistant than 50 years and below age group (OR=3.37, 95%CI; 1.19 – 9.54).

4. DISCUSSION

Current Patterns of Antibiotic Prescriptions

Among the total 781 antibiotic prescriptions, surgical prophylaxis, 257 out of 781, (32.91%) was the most frequent indication among study participants. Community-acquired infection was the third most prescribing indication with 21.13 %. The second most frequent indication was other category with 32.27% which includes non-communicable diseases, minor injuries, and might be a result of inaccurate information from patient's medical records. These results slightly differ from another study, (Oo et al., 2022), which expressed that the highest prescribing indication was community-acquired infection (44.6 %), and surgical prophylaxis was the second most frequent (34.3%). Surgical prophylaxis was the leading indication in this study which pointed out that the requirements of antibiotics for surgical prophylaxis should review in military healthcare settings. The study was carried out in a tertiary military hospital and there might be more trauma and warfare injuries than in a civil tertiary hospital.

Cephalosporins were the most prescribed antibiotic class (33.42% of the total prescription) followed by Penicillins (19.85%). The similarity was found in another study conducted in Myanmar, (Oo et al., 2022), which stated that the leading use of antibiotics was third-generation Cephalosporins. The findings from the India study also showed that third-generation Cephalosporins (18.48 %) were the most prescribing antibiotic while Metronidazole stood at the fourth-most (14.65%) (Williams et al., 2011). The findings indicate a proper antibiotic stewardship program to review periodically the most prescribing antibiotics as hospital routine.

Only a tiny minority, 65 out of 441 study participants, (14.74%), underwent culture and sensitivity tests. The finding is lower in contrast to the findings from other studies, (43%) in Denmark (Sydenham et al., 2021), (48.8%) in Indonesia (Limato et al., 2021). However, the results are better than the culture sample taking data from other studies, no culture and sensitivity test for all prescriptions in Ethiopia (Demoz et al., 2020), (2.7%) in Ghana (Amponsah et al., 2021), and (14%) in Tanzania (Horumpende et al., 2020). Low culture and sensitivity tests might be the result of urgency of treatment, underutilized laboratory by prescribers, limited resources in the laboratory department, and time-consuming and delay results from the laboratory.

Among the culture test underwent participants, 34 out of 65 (52.31%) were multidrug-resistant. The finding of the MDR rate was higher than the multidrug-resistant data of other studies, 10% of Pseudomonas aeruginosa, 36% of Klebsiella pneumonia among healthcare-associated infections in Thailand (Lim et al., 2016), 42.1% of Enterobacteriaceae in Ethiopia (Bitew & Tsige, 2020), However, the finding is lower than 67.1% MDR rate in Bangladesh (Alam et al., 2021). High MDR data might be a result of improper prescription (such as wrong antibiotic choice, wrong time of prescription, wrong dose, wrong duration and wrong route of administration, and wrong time to stop or review), high infections rate, and presence of counterfeit and substandard drugs.

The Proportion of Multidrug-Resistant Gram-Negative Bacteria from Clinical Samples Obtained from the Study Population

Among the culture test-underwent participants, nearly fifty percent expressed gram-negative microorganisms. The leading microorganism was Klebsiella pneumonia (45.16%) followed by pseudomonas aeruginosa (22.58%). These findings were slightly different from the results from the study conducted in Ghana which revealed the most frequent gram-negative organism was E.Coli (24.5%) followed by P. aeruginosa (19.5%) and K.pneumoniae (19.0%) (Agyepong et al., 2018).

Among the gram-negative microorganisms, 28 out of 31 (90.32%) revealed MDR. This result was higher than MDR among gram-negative organisms in other studies, (26.16%), (32.98%) and (33.33%) in India (Nagvekara et al., 2020), (48.8%) in Thailand (Chaisathaphol & Chayakulkeeree, 2014), and (66.0%) in Bangladesh (Alam et al., 2021). The high MDR rate of gram-negative microorganisms pointed out the alarming signal of threats of gram-negative microorganisms and relevant prevention, control, and therapeutic measures should be encouraged.

The Presence of Class 1 Integron Gene among Isolated Gram-Negative Bacteria

Among the gram-negative bacteria, 17 out of 31 (54.84%) were class 1 integron positive. The finding was higher than the class 1 integron positive rate among gram-negative organisms in other studies, 26.5% for E.coli in China (Huang et al., 2020), 31.8% in the IRIS study (Barraud et al., 2022), 33.3% for P.aeruginosa, and 33.3% of A.baumannii in Iran (Moosavian et al., 2018), and 41% in Iran (Pormohammad et al., 2019). However, the finding was lower than the results of other studies, 59% in Russia (Kuzina et al., 2019). The high results of class 1 integron positivity among gram-negative organisms might be a result of inadequate gram-negative samples in the present study.

The proportion of class 1 integron in MDR was (60.71%) in this study. This finding was lower than the findings from other studies, (79%) in Iran (Pormohammad et al., 2019). The finding was similar to (67%) class 1 integron in MDR (Al-Hammadi et al., 2020). The result of the current study is higher than (Huang et al., 2020), in which (45.5%) of class 1 integron among MDR in China. Class 1 integron positivity among MDR in the current study might be lower than in the other studies as a result of limited culture tests leading to few gram-negative organisms in the study.

The Association Between Antibiotic Resistance and The Presence Of Class 1 Integron

The association between class 1 integron and multidrug-resistance showed a positive association between class 1 integron and multidrug-resistance but it was not statistically significant X^2 (1, n=31) = 4.033, p = 0.081. This finding was different from the results of other studies, the negative predictive value of class 1 integron as a marker of antibiotic resistance was estimated at 92.8% in the IRIS study (Barraud et al., 2022), and the 95% of multidrug-resistant isolates were class 1 integron positive revealing statistically significant association between multidrug-resistance and the presence of class 1 integron (Win, 2021). The association between class 1 integron and drug resistance was expressed in numerous research and literature but there was no statistically significant association between class 1 integron and antibiotic resistance in the present study. The result might be a consequence of the limitation of the study where a few culture samples were sent to the laboratory leading to few numbers of gram-negative organisms in the study. The few gram-negative organisms in the present study cause failed to meet the adequate number to find out the association between class 1 integron and antibiotic resistance.

Three and more antibiotic prescriptions, surgical prophylaxis, and old age group were positively associated with multi-drug resistance with (AOR=8.9, 95% CI; 2.3-34.2), (AOR=21.1, 95% CI; 2.1-210.0), and (AOR=4.6, 95%CI; 1.2-17.2) respectively. A wide range of confidence interval of AOR might be a result of a few samples of culture testing from which the outcome variable for logistic regression, multidrug-resistance, was calculated. This finding accorded with the global contributors to antimicrobial resistance by (Chokshi et al., 2019) which stated that clinical misuse, ease of antibiotic availability, and poor hospital-level regulation were the main contributors to antibiotic resistance.

There are some limitations to the study. First, the coincidence of the study period with the COVID-19 pandemic and purposive sampling of one tertiary military hospital so that the findings from the study may not reflect all military hospitals. Second, we collected data at a certain point in time resulting in that duration of antibiotic prescription was not measured. Third, some health care professionals might probably miss writing down indications or reasons for antibiotic prescription in the chart which leads to misinterpretation in the study. Fourth, the culture taken among study participants was under-investigated which might lead to over or underestimating the actual prevalence of gram-negative microorganisms. Fifth, class 1 integron was tested among a few amounts of gram-negative microorganisms so that the association between multidrug resistance and class 1 integron might be underestimated.

5. CONCLUSION

Antibiotic consumption rate, the percentage of three or more antibiotic prescriptions was higher than WHO standard indicators and the findings from the other studies. Therefore, antibiotic policy and standard treatment guidelines for the tertiary military hospital should be developed while surveillance of antibiotic resistance must be performed simultaneously.

Only a tiny minority underwent the culture and sensitivity test. The antibiotic prescription should be the right choice for the infection so that culture and sensitivity tests of the high antibiotic consumption wards of the tertiary hospital should be promoted. Moreover, resources such as microbiologists, expert laboratory technicians, quick and simple technology, and machines, should supply to the laboratory department.

6. CONFLICT OF INTEREST

The authors declared that they have no conflict of interest.

7. ACKNOWLEDGEMENT

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